DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1965

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

EIGHTY-EIGHTH CONGRESS

SECOND SESSION

SUBCOMMITTEE ON DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE AND RELATED AGENCIES APPROPRIATIONS

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WINFIELD K. DENTON, Indiana
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ROBERT M. MOYER, *Staff Assistant to Subcommittee*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Part 3

National Institutes of Health

Printed for the use of the Committee on Appropriations

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DEPARTMENTS OF LABOR, AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1965

TUESDAY, FEBRUARY 25, 1964.

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. STUART M. SESSOMS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS, NATIONAL INSTITUTES OF HEALTH
DR. JOHN F. SHERMAN, ASSOCIATE DIRECTOR FOR RESEARCH GRANTS AND AWARDS, NATIONAL INSTITUTES OF HEALTH
RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH
B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
DR. LUTHER L. TERRY, SURGEON GENERAL
HARRY L. DORAN, CHIEF FINANCE OFFICER
JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Mr. FOGARTY. The committee will come to order.

We shall begin our hearings with the National Institutes of Health this morning. Dr. Shannon I believe you have a statement for the committee.

Dr. SHANNON. Yes, Mr. Chairman, I have a fairly long statement but one that covers most of the major issues that would be of interest to the committee. I thought it might be helpful to the committee if we go over those first and clear the way for examination of the Institutes' projects, more in terms of the substance of their program, rather than general policy issues.

Mr. FOGARTY. All right, go ahead.

Dr. SHANNON. All right.

GENERAL STATEMENT

The Chairman and members of the committee, in each of the 9 years that I have had the privilege to come before this committee, my purpose has been essentially the same, to report to you—in clear and candid terms—on the progress and further needs of our national health research efforts.

However, from year to year, I find it increasingly difficult to present for this committee a review of National Institutes of Health programs and activities that is meaningful and reasonably complete, and—at the same time—succinct. Inevitably I intrude too long on your attention—or omit that I feel you ought to hear. I don't pretend, therefore, that today's compromise satisfies me; but I trust it will meet your main needs for general information.

I propose to limit myself, even more strictly than in the past, to a very few program and administrative highlights. That will permit me to give most of my attention to what I consider to be the key problems and issues, and also the future prospects, in each of our major program areas. By omission, that leaves a number of important program aspects for which I hope you will look mainly to the Institute and program directors who will be following me as witnesses. By this division of labor, you will look to them for the status of research in major disease areas, highlights of scientific accomplishment, and systematic review of special programs.

OVERVIEW OF 1965 BUDGET REQUEST

It is important at the outset to present an overview of the fiscal 1965 budget request which is now before the committee. For the 10 operating appropriations through which NIH supports health research and training, we are requesting $957.4 million for fiscal 1965. This works out to an increase of $65.2 million, or slightly more than 7 percent, over estimated operating levels for the current year. For health research facilities construction, the separate appropriation request is $58 million. This adds $2 million to the comparable 1964 total for mental retardation research facilities.

GROWTH RATE OF PROGRAMS

By comparison with appropriation increases of recent years, the requested increase for this year is modest indeed. For that reason, I am sure that the members of this committee will be concerned to hear whether we risk loss of momentum on these health research programs, which over the years have owed so much to congressional leadership.

If these programs are growing at a slower rate than in the recent past, this reflects a rather special stage of development through which these programs are passing. For program managers, the past year and year ahead represent periods of introspection as well as action. There are major new programs to be planned and mounted. Many program goals and mechanisms are being rethought. And as you well know, broad reviews of Federal science support programs and policies are underway on both executive and legislative fronts. These reviews, I might say, provide a most useful occasion for our taking a penetrating look at the full range of what we are doing now—and what needs to be done. From our current study of programs, including goals, means, policies, magnitude, impact, and accomplishments, I am confident will emerge strengthened efforts for tomorrow.

I want to add one note of caution on 1965 totals: the increases we are proposing are minimal. The estimates behind them are as tight and as hard and as realistic as we could make them. In a word, we have left ourselves slim margins, or none, whether for regular project grants or for the major new programs getting underway. I hope, therefore, that you will continue to allow us a degree of flexibility in use of funds within a single appropriation. Such flexibility, I am convinced, is a key to the effective management of our programs in a tight budget situation.

DISTRIBUTION OF PROGRAM EFFORT

For fiscal 1965, we plan to distribute program effort in this manner: The total in 10 operating appropriations, $957.4 million, breaks down into research support of 57.7 percent, training 23.6 percent, NIH direct operations 18 percent, and State control programs 0.7 percent.

Mr. Fogarty, I would like to submit for the record, if it has your approval, a more detailed breakdown of those figures.

Mr. FOGARTY. All right.

(The matter referred to follows:)

For fiscal year 1965, we plan to distribute program effort in this manner:

	Percent
Total in 10 operating appropriations ($957,400,000)	100
Research support	57.7
Regular research grants ($440,200,000)	46.0
Special research grants ($72,000,000)	7.5
General research support ($40,000,000)	4.2
Training	23.6
Training grants ($180,000,000)	18.8
Fellowship programs ($45,700,000)	4.8
NIH direct operations	18.0
Direct research ($76,100,000)	7.9
Collaborative research ($64,400,000)	6.7
Biologics standards ($5,000,000)	.5
Other direct ($27,300,000)	2.9
State control programs ($6,800,000)	.7

Most of the additional funds we are requesting for next year will go to our regular research grants programs. For these, the increase over estimated operating levels for 1964 is $34.5 million. We are projecting funds for completely new awards in 1965 at the same level as in 1964; but the increase will be needed for the higher cost and greater number of research projects now active for which support will be continued in fiscal year 1965. Indirect costs for research grants will also rise by an estimated $7.5 million. You will note that as of January 1, 1965, we are showing a new indirect cost rate of 25 percent instead of today's 20-percent rate. This, I understand, represents a uniform policy for all similar Federal programs.

Among special research grant programs, we are proposing two moderate, and several quite minor, increases over 1964 operating levels. An additional $5 million for our general research support grants program will bring that program total to $40 million. This will permit extending this important form of support to a number of new institutions which will become eligible in fiscal year 1964. We are also proposing $6 million more for the National Institute of Mental Health program of hospital improvement grants that got underway this year. Minor increases include $1.3 million for increased operating costs of primate centers; and the general and categorical clinical research centers programs, taken together, will receive about $800,000 more to cover increased costs as the present level of the program is consolidated.

For the very important training program area, we are asking an additional $12 million; or about 5.5 percent above estimated operating levels for 1964. Eight million of this will help meet acute shortages of mental health personnel—particularly service personnel for the new community mental health centers. The only other sizable increase—$1.5 million—is to National Institute of General Medical Sciences with its key training programs in basic life sciences. Among fellowship programs, a rise in predoctoral stipends to meet higher training costs adds an estimated net increase of $735,000 for the predoctoral fellowship program—mainly going to the National Institute of Mental Health and the National Institute of General Medical Sciences.

Finally, $7.2 million above 1964 operating levels will go to NIH direct operations—providing moderate expansion of NIH intramural research and National Cancer Institute collaborative studies—3.7 and 4.7 percent increases, respectively.

There is one significant decrease in the 1965 request: $4.2 million less will be needed for the State control programs, due to the discontinuance and completion of the program for National Institute of Mental Health State planning grants.

RECENT ORGANIZATIONAL AND ADMINISTRATIVE CHANGES

I should like now to review briefly some organizational, administrative, and staff changes at NIH during the past year.

Last February, Dr. Ernest Allen, who has been associated with the NIH research grants program since its inception, moved from his post as NIH Associate Director to the position of Grants Policy Officer in the Office of the Surgeon General. Dr. Martin Cummings, who filled creditably two exacting jobs—as NIH Associate Director for Research Grants and Chief of the Office of International Research—was selected this past December to become the New Director of the Library of Medicine.

To succeed Dr. Cummings in the international area at NIH, Dr. Charles Kidd has moved from NIH Associate Director for Training to the new post of NIH Associate Director for International Activities. Dr. Kidd, as you may recall, has had long experience and continuing interest in international aspects of health research so that we may count on these programs being in good hands.

The retirement of Dr. Dale Lindsay, Chief of the Division of Research Grants, brought to that key position an able replacement in Dr. Eugene Confrey. For his many services to the Public Health Service, Dr. Lindsay received the Meritorious Service Award.

Finally, I would like to mention the recent appointment of Dr. John Sherman to the new post of NIH Associate Director for Grants and Awards.

In this capacity, Dr. Sherman will bear the main staff responsibility in both research grant and training areas. Dr. Sherman, who joined

NIH in 1956, comes to this new post from his former position as Associate Director for Extramural Programs, National Institute of Arthritis and Metabolic Diseases.

Several other items from the administrative areas may interest you.

ADDITION OF TWO NEW INSTITUTES

Clearly one of the most significant events for health research in recent years was the addition of the two new Institutes authorized by Public Law 87–838. Their formal establishment took place last February. This year, therefore, has been an exceptionally busy one, particularly for the completely new Institute of Child Health and Human Development. This Institute has had to define and plan a new series of programs in terms of a new program concept—the study of human development over the full life span. Other tasks have included identifying existing grants and programs relative to this life-study context, and negotiating for their transfer from other Institutes; planning for the new mental retardation research centers authorized by Public Law 88–164; and, of course, the unavoidable housekeeping tasks of organizing the new Institute, and recruiting staff, particularly scientific program managers. To the rest of us at NIH, Dr. Aldrich, our able young Director of National Institute of Child Health and Human Development, has seemed easily the busiest man on the reservation.

Because the National Institute of General Medical Sciences represents mainly a new status for a series of on-going programs and activities, Dr. Powell, the Director of our other new Institute, has been able to focus his efforts on a somewhat narrower range of urgent needs. Redefining and reorganizing of programs has been one of these. This need arises in part from the substantial program transfers over the past 18 months to National Institute of Child Health and Human Development, Division of Research Facilities and Resources and other Public Health Service components; and in part to the inescapable fact that new areas of promise and interest in the basic life sciences evolve at an exceptional pace. The National Institute of General Medical Sciences also is planning a major new effort in pharmacology and toxicology research. Recruitement of scientific program staff—depleted by program transfers—has been a second major area of concern for Dr. Powell.

I am sure that the members of this committee will find much to interest them in the reports on the new Institutes they will be hearing shortly from Dr. Powell and Dr. Aldrich.

HEALTH RESEARCH LEGISLATION

I also want to underline one evident and very happy fact: 1963 has been a most favorable year for health research legislation. For example, Public Law 88–164 stands out as a health landmark. Dr. Felix will have much to say to you about the community mental health centers authorized by this new public law; and Dr. Aldrich will want to describe his plans for carrying out the new authority for mental retardation research facilities. I will mention two other public laws from which I also see benefits flowing far into the future: The Health

Professions Educational Assistance Act (Public Law 88–129) is one of these. This act is basic to our assuring manpower for health and health research needs for the future. Public Law 88–204 is a companion act to this one. It launches a massive $1.2 billion program of teaching facilities construction to do for other fields of higher education what Public Law 88–129 attempts for the health professions alone. I may say that we are equally gratified by the passage of both public laws. If the promise from health research—or in any other science area—is to be fulfilled, we recognize that our total educational system, at all levels, must be honed to a new state of effectiveness. We cannot afford to waste any of our best intellects, either through failure to identify them, or through education inferior to their promise.

INTRAMURAL RESEARCH STAFF

For our intramural and related science activities at Bethesda our main program concern has always been this: to assure maintenance of an intramural research effort of acknowledged excellence, imagination, and drive. I see no alternative to this because:

First, NIH intramural programs are the largest biomedical research effort in the world. Clearly there is an obligation, both to the public, in terms of public funds spent, and to the scientific community, in terms of the significant percentage of total national science talents drawn upon, that these efforts reflect highest possible standards of excellence.

Second, excellence intramurally is a precondition for the successful operation of the extramural programs. Only with this excellence recognized can we count on the judgments of the NIH professional staff gaining ready acceptance within the biomedical community, as those of a respected peer group.

Finally, major collaborative and developmental research programs, which are planned and directed from Bethesda but may have important research contract and research grant components, are particularly demanding of strong and knowledgeable science leadership from NIH scientists.

Several steps taken during the past year to maintain conditions favoring research excellence at Bethesda merit notice. In September, the unique new surgical wing for the Clinical Center was dedicated. After disappointing delays, we now have in Bethesda—mainly for heart and brain surgery—what we believe to be the exciting prototype of surgical suites of the future.

Another valuable resource, being readied oncampus for our intramural scientists, is a pathogen-free animal colony. I note, also, that phase I construction has started at the Animal Center in Poolesville. This will add farm animal and dog quarantine facilities along with utilities and various support structures. I might add, that during the calendar year 1964, we are hopeful that ground will be broken for the National Cancer Institute intramural research building and the National Mental Health-National Institute of Neurological Disease and Blindness intramural research building.

PAY FOR KEY SCIENTISTS

The main threat to retention of intramural research excellence at Bethesda, though serious indeed, continues in chronic rather than acute stage. This threat lies in our inability to pay a relatively small number of key scientists a salary that is comparable to what they can command—and frequently are offered—by certain universities or concerns from the private sector. Our worry is for the exceptional scientists whose presence acts to guarantee a strong program—through their ability to attract, and to hold, outstanding younger scientists; and whose departure from a program, by reverse attraction, may leave behind only an empty program shell in a key science area. This problem is not localized to any specific NIH program or disease area; nor would I expect it to be limited to health research alone among Federal science support programs. But the solution to this problem, as I view it, can only be legislative.

With today's keen competition for scientists of proven insight and effectiveness, the staffing of a completely new Institute such as National Institute of Child Health and Human Development presents a rather special problem. I think that in the face of this, Dr. Aldrich has accomplished much in a short time. I will mention, though, an early suspicion that has grown to a clear concern in this recruitment effort. It is now apparent that the lack of an intramural research program—which we felt initially would not be needed—has handicapped NICHD in its efforts to obtain certain of the scientific program managers it has most wanted. This fact could have serious impact on the future stability and success of NICHD programs. For that reason, we are studying this problem with Dr. Aldrich, and are considering possible solutions both for the immediate and foreseeable future.

I might add that personnel shortages in the category of the advanced professional continue to hamper the development of many areas in th extramural program. Such a situation not only slows down or prevents the early establishment of urgent new programs, but it also handicaps the continued evolution of programs already in being, curtailing to an indeterminate degree their effectiveness.

AWARDS RECEIVED BY NIH SCIENTISTS

Of the many awards and honors received by NIH scientists during the past year, I will only mention a few, and Mr. Fogarty, if I may——

Mr. FOGARTY. Put them all in the record. Mention a few of the most outstanding and put the rest in the record.

Dr. SHANNON. I will point out those that have broad impact across many contiguous science areas.

For example, awards have been received by Dr. Marshall Nirenberg and Dr. Bernard B. Brodie, both of the Heart Institute. These awards recognized the enlightened research approach and the dramatic results of Dr. Nirenberg in his clarification of the mechanics through which information is passed from mother to daughter cell through genetic material contained therein. And Dr. Brodie, on the other hand, has been outstanding for some 10 years in evolving a more rational approach to the study and development of new therapeutic agents. Again, Dr. Brodie's work has had a pronounced effect on many contiguous areas of science.

I could mention other awards individually, but will only call to your particular attention those for Dr. Masland and Dr. Felix, two of our Institute directors. The award for Dr. Masland was made by President Kennedy himself, on behalf of the National Society for Retarded Children, for the work he has done over the past decade in creating awareness of this mental retardation problem and development of programs to combat it.

Dr. Felix received the Nolan D. C. Lewis Award for his outstanding contribution to psychiatry. This recognizes the part he has played in developing broad public awareness of the problem and in developing a legislative basis and coordinated public and private group efforts for the ultimate solution of the problem.

Again, I would point out that these two awards, Dr. Masland's and Dr. Felix's, are broad awards in recognition of national public service.

With your permission, Mr. Fogarty, I will place in the record the listing of the other awards. I might say, however, that it is very gratifying to the National Institutes of Health to see these individuals get truly national recognition for the outstanding job that they are doing. I think that this recognition attests in a very striking way to the excellence of the NIH scientists supported and to the effectiveness of the NIH programs.

(The information referred to follows:)

AWARDS AND HONORS, 1963

Dr. Francis A. Arnold, Jr., director, NIDR: 1963 Callahan Award, highest honor by Ohio State Dental Association for person who has made a contribution of exceptional value to dental science. Wm. John Gies Award: "In recognition of his distinguished career as a scientist and research administrator, and for his contributions to dental research and public health."

Dr. James E. Birren, NIMH: New York City Award for Research in Aging, by Senior Sixty-Fivers of District 65, wholesale-retail department store union.

Dr. Nina Braunwald, NHI: Named "Woman of the Year" by the Silver Spring Business and Professional Women's Club.

Dr. Bernard B. Brodie, NHI: Torald Sollmann Award in Pharmacology ($2,500 and inscribed medal).

Dr. Thomas D. Dublin, NIAMD: One of first four recipients of Hadassah's "Myrtle Wreath for Distinguished Achievement" given for role as a principal coinvestigator in long-range study of heart disease in Israel.

Dr. Robert H. Felix director, NIMH: Nolan D. C. Lewis Award for "outstanding contributions to psychiatry"; Salmon Medal for outstanding contributions to science and humanity given by New York Academy of Sciences; the Edward A. Strecker Medal for outstanding contributions in the field of community mental health services.

Dr. Seymour Geisser, NIAMD: Elected to fellowship in the American Statistical Association. Citation received: "For his contributions to the methodology of multivariate analysis and its application in the behavioral sciences; for his superior service as a consultant to scientists in medical, biological, and chemical research."

Dr. Carleton Gajdusek, NINDB; E. Mead Johnson Award from the American Academy of Pediatrics for his studies on children in primitive societies, viral, and other neurological diseases.

Dr. Wilhelm C. Hueper, NCI; chosen by editorial board of Modern Medicine as 1 of 10 recipients of magazine's annual distinguished achievement awards.

Dr. Leon Jacobs, NIAID; Henry Baldwin Ward medal and $1,000, by the American Society of Parasitologists in recognition of his distinction as a world authority on the biology, epidemiology, and laboratory diagnosis of toxoplasmosis.

Dr. Sanford Kuvin, NIAID; Frederick Murgatroyd Award presented by University of London to best student earning an academic postgraduate diploma in clinical medicine.

Dr. Marshall W. Nirenberg, NHI; Paul-Lewis Award ($1,000) by the American Chemical Society for research in enzyme chemistry.

Dr. Richard L. Masland, director, NINDB; Annual Award of Merit, National Association for Retarded Children, for achievements in alleviating the problems of mental retardation.

Drs. Howard A. Moss, and Jerome Kagan, NIMH; Shared (with a grantee team) the American Psychiatric Association annual Hofheimer Prize ($1,500) for research in the fields of posthospital experience and child development.

Dr. Frank J. Rauscher, NCI; Comenius Alumni Award of the Moravian College Alumni Association.

Dr. Nelson K. Richtmyer, NIAID; Claude S. Hudson Award, conferred in recognition of outstanding contributions in the field of carbohydrate chemistry.

Dr. Paul A. Di Sant'Agnese, NIAMD; Awarded honorary doctor of medicine by the Justus Liebig University of Giessen, Germany. Fourth American to be so honored.

Dr. Arthur L. Schade, NIAID; Medal of Honor of Milan University at the Instituto di Chimica Biologica dell 'University di Milano, Italy.

Dr. David Shakow, NIMH; Stanley R. Dean Research Award, $2,000 grant by the Fund for the Behavioral Sciences to stimulate research into schizophrenia.

Dr. Maxine Singer, NIAMD; Iota Sigma Phi research award for outstanding work in biochemistry. Prize includes a $300 honorarium. Award given only to women under 40.

Dr. Albert Sjoerdsma, NHI; Award given by the American-Swiss Foundation for Scientific Exchange, Inc., to be honorary lecturer at medical schools in Geneva, Lausanne, Zurich, Basle, and Berne.

Dr. Milton W. Skolaut, chief pharmacist, CC; Geigy Leadership Award from the Geigy Pharmaceutical Co., "for outstanding leadership in the field of hospital pharmacy and for his personal achievement and exemplary direction of the CC Pharmacy, which sets the pace and standard of hospital pharmacy in this country and abroad."

Dr. Sarah E. Stewart, NCI; G. Lenghi prize for 1963 by the National Academy of Lincei, Rome, Italy. Two million lire (about $3,000) given biennially to an investigator who has made important scientific contributions in the field of oncology.

Dr. Martin D. Young, NIAID; Darling Foundation medal and $1,000 Swiss francs by the World Health Organization, for outstanding accomplishment in the field of research in malaria.

EXTRAMURAL PROGRAMS

I would like to turn to the extramural programs now, and say that in its relations with the larger biomedical research community, NIH has two main concerns:

1. To assure a comprehensive range of imaginative and well thought-out programs that constructively advance biomedical research. These programs are judged by the sensitivity with which they identify, and meet, the current needs and opportunities of the biomedical research community. I feel that in this aspect of our extramural activity, NIH has done rather well, despite the continuing limited availability of high-level professional personnel.
2. To take into account, and reconcile, the divergent roles and responsibilities of a Federal science support agency, that is, NIH, of grantee institutions; and of individual scientists. The imperative here is to strike a balance favorable both to the obligations of public stewardship, and to the demands of scientific creativity. The administrative complexities of NIH programs arise mainly on these points. We have learned a great deal in the past few years about the issues here, and about how to resolve them. On the whole I think we are progressing satisfactorily in this area, too.

STRENGTHENING GRANTS ADMINISTRATION

During the past year, these have been the main steps taken by the Public Health Service to strengthen grants administration:

Of paramount importance was the codification of conditions of grant awards and their issuance in manual form. A second edition of this research grants manual will go into effect April 1, 1964. The conditions covering all Public Health Service training grants have now also been codified and will be issued in manual form.

The Division of Research Grants of the National Institutes of Health was designated as single grants manager for the Public Health Service.

Functions of the new Grants Policy Office, in the Office of the Surgeon General, have been delineated, and staffing of the Office has been strengthened.

A plan for the transfer to grantees of certain routine administration decisions on grants has been developed by our staffs. Formal review mechanisms in grantee institutions, plus Public Health Service approval of these institutional arrangements will be preconditions to exercise of this delegation. A trial run of such operations is in the course of current planning.

A study looking to standardization of stipends, particularly at the predoctoral level, has been completed.

In evaluating NIH activities in this extramural area, the several levels from which these activities can be viewed should be kept fully in mind. The soundness of management policies and practices is a legitimate level of concern; so is the qualitative nature of the work of individual scientists supported. I would like to suggest, however, that the overriding concern should be this: the degree to which the entire scope of NIH activities has advanced national scientific capability in understanding the nature, the cause, the treatment and the prevention of disease.

TRAINING PROGRAMS

The main annual investment in the future of health research in this country is in the NIH training programs. From these programs rise our best hopes that the biomedical community will receive a steadily increasing input of fresh intellects, fresh energies, and fresh ideas—and technical competence to carry them productively forward.

To sustain this essential input, we are requesting $225.7 million in training and fellowship funds for fiscal year 1965. This represents an increase of roughly $12 million—or 5.5 percent above the 1964 operating levels—with $8.3 million of the increase going to National Institute of Mental Health, and about $2 million to National Institute of General Medical Sciences and the remainder being distributed among the other institutes.

Investment in training research manpower for the future continues to comprise about one-quarter of our total program effort. Roughly 5 cents out of every NIH program dollar will go for fellowships or similar training awards to individuals; another 19 cents out of every program dollar will go for training grants to institutions. Nearly 9,000 individuals at the predoctorate level, and about 5,500 at the postdoctorate level received some form of training under these programs in 1963.

I might point out that these figures must be viewed not as annual production figures of trained scientists, because at the predoctorate level, the scientists would be supported for 3, perhaps 4 years; at the postdoctorate level, more than 1, usually 2. So that the number of trained scientists that are emerging from the training program is substantially less than the number I have mentioned.

Furthermore, a number of the individuals who are supported at the predoctorate level at a later time receive highly specific training at the postdoctorate level. So that one must view these training figures as what is contained in the pipeline now, to become available at different times and at different stages of scientific development.

Our medium-range goal in training continues to be a doubling of medical research manpower during the decade 1960 to 1970. At this point, I cannot confidently assert we will hit that mark, but we hope to approximate it.

These additional points about our training activities may interest you:

I anticipate great gains from the pioneering medical scientists training program for which the National Institute of General Medical Sciences made its first awards this year. This program aims at an urgent need: the development of well-rounded medical scientists. Individuals chosen for this program combine training in the traditional medical sciences with thorough studies in mathematics, and physical and biological sciences. Many if not most of these graduates will receive serially or simultaneously M.D. and Ph.D. degrees. So far, two awards have been made under this program. I am pleased that the National Institute of Arthritis and Metabolic Diseases and National Institute of Child Health and Human Development are also launching medical-scientist training this year—with parallel programs but oriented more closely to specific Institute needs.

For 1965, 294 senior investigators in universities and medical schools across the country will be receiving long-term salary support through NIH Research Career Awards. This program, now in its third year, provides career-minded investigators with full salary support at grantee institution scales. The Career Development Award program—aimed at an earlier, and perhaps the most productive phase of research careers—provides stable salary support for 930 investigators. Twenty-one million dollars is the approximate annual cost of the two parts of this program today.

With a view to standardizing training stipends, particularly at the predoctoral level, the Public Health Service studied levels of stipends and the relationship between training grants and fellowships this year. Twelve Public Health Service teams visited 34 grantee institutions—mainly graduate schools, and medical schools—interviewing key individuals, following a uniform questionnaire. Our conclusions from this study underpin a number of the policies and procedures you will find in the new training grants manual that we expect to issue this spring.

INTERNATIONAL ACTIVITIES

Dr. Kidd, our new Associate Director for International Activities, will describe for you our special international programs, and will identify the specific research gains and problems we are experiencing with them. I will merely note that for the foreseeable future, what we can do in this international area must be done within limits set by the U.S. balance-of-payment situation. The unmistakable trend of our international programs, therefore, is downward.

The budget before you contains approximately $13.5 million for research grants to foreign institutions and investigators. This is $1.5 million less than the $15 million operating level estimated for oversea research support in fiscal year 1964. All of this year's decrease will take place in the economically advanced countries, such as Western Europe, in which gold-drain problems are most acute. This is in accord with executive department policy.

We continue hopeful, though, that it may be possible to stabilize these international programs at a point where needs of national monetary policy are met, and yet we are able to capitalize on some of the unique research opportunities we seek. I may say that President Johnson's warm endorsement of international medical research in his health message encourages us to believe that such a stabilizing point may be found.

I remind you what we seek through these international programs is this: there are many insights into disease that can only be provided by variations in ethnic, climate, diet, behavioral or ecological factors which require observation and study in other countries. Also, we seek the always valuable stimulus of first-rate intellects and first-rate research ideas—of which no nation ever has enough, nor any nation can claim a near monopoly. Finally, I would emphasize that this is a program aimed at satisfying our own domestic needs in a purposeful manner and should not be viewed as one oriented in whole or in part by concepts of foreign aid.

NEW PROGRAMS

Turning to new programs: Several highly significant new programs are scheduled to get underway this year. I know you will want to hear our plans for accomplishing this. By the division of labor I referred to earlier, you will receive most of the interesting details on this from Dr. Felix, Dr. Aldrich, and Dr. Arnold, who are the Institute Directors immediately concerned. I will prepare the way for these fuller discussions by identifying the programs, by stating why I consider them significant, and by suggesting how they fit into total NIH efforts. These are the programs:

Community mental health centers, for which Dr. Felix is responsible.

Mental hospital improvement program, also Dr. Felix.

Centers for research on mental retardation and related aspects of human development; this is Dr. Aldrich's responsibility.

Dental Research Institute for which Dr. Anold is responsible.

COMMUNITY MENTAL HEALTH CENTERS

I want particularly to say a word or two about the community mental health centers program. I view this as perhaps the most important and promising effort to solve our mental health problems since the creation of the Mental Health Institute itself. I hope that members of this committee—and other congressional representatives as well—will take a personal interest in these centers. This is a Federal-local cooperative effort with the main cost burden resting locally. Its success or failure, therefore, will be determined largely by what is done or not done at the community level, where your support and concern will be most constructive.

As you may recall, the recommendation for a comprehensive mental health effort—community based—came from a special commission appointed by the President. The initiatory step was a $4.2 million program of planning grants, to aid State and local governmental units in working out program proposals. With the enactment of Public Law 88–164, we now have the basic authority to proceed, plus a Federal commitment of $150 million for the brick-and-mortar portions of the program. A great deal remains to be done, as I am sure Dr. Felix will make clear to you. I may say that in my view Dr. Felix has performed magnificently in the initial phases of this program. He will be working now—with his own staff and those in many communities throughout the country—to assure that the brick-and-mortar shell will be filled with program content equal to the problem.

MENTAL RETARDATION RESEARCH CENTERS

The mental retardation research centers similarly received their basic authority from Public Law 88–164, and similarly consist now of a Federal commitment to construction funds. This, of course, is a smaller program than Dr. Felix's—though one of great importance—and Dr. Aldrich will be able to follow patterns established on earlier NIH centers programs. The construction funds—$6 million this year and $8 million asked for next year—will actually be handled by Dr. Stone, as parts of health research facilities construction. Dr. Aldrich and Dr. Stone will work together on problems of design of these centers, and Dr. Aldrich will work with grantees to assure an effective research attack on mental retardation. Although the National Institute of Child Health and Human Development—among NIH Institutes—will have the broadest program interest in mental retardation—and, therefore, in these centers—important support for certain aspects of research will also come from other Institutes—particularly the National Institutes of Mental Health and National Institute of Neurological Diseases and Blindness. Other sources of research program funds are expected to be the grantee institution and foundations or voluntary agencies.

DENTAL RESEARCH INSTITUTE

With respect to the dental research institute program, I note that here, too, the key to program initiation is construction funds. Dr. Stone has been cooperating with Dr. Arnold, Director of National Institute of Dental Research, to assure that health research facilities funds are available to support this effort. I might say that so far with this program we have not aroused the degree of interest in the specific quarters that we had hoped for. The intent, as you will recall, is not merely to add an extra dimension to existing dental efforts, though this is not precluded per se. The real hope is to focus multidisciplinary scientific interest on the full range of dental problems, much as is done in the National Institute of Dental Research itself. This could be accomplished, I feel, in any major university with strong biomedical research departments.

MENTAL HOSPITAL IMPROVEMENT PROGRAM

The mental hospital improvement program, which was funded for the first time in this fiscal year, is distinctive to National Institute of Mental Health activities. It provides $6 million this year, and asks $12 million for next year, for incentive grants to State mental hospitals. Its objective is to help these hospitals break the dominating pattern of custodial care, and to stress treatment and rehabilitation instead.

GUIDING PRINCIPLES OF NIH PROGRAMS

I should like now to turn my attention to certain broader aspects relating to the further development of NIH programs and of medical research generally. I may say that I am struck—and doubtless you have been, too—at the significant change even a few years makes in these programs. Not only do program topics succeed each other steadily, but, also, and quite perceptibly, there are shifts in the perspective from which both we and others view NIH efforts.

I no longer feel the need to take up, in any detail, many of the topics that claimed our attention in previous years. Due in large part to the broad context in which this committee has viewed NIH activities, there is a fairly clear consensus, and little need for additional debate, on the essential principles now guiding the development of these programs. I note little disagreement, for example, on the need to support research in the fundamental sciences as a means to advance disease research; nor on the importance of a diverse portfolio of imaginative programs and support devices to meet changing needs of our biomedical community; nor on the imperative of expanding future research capabilities through support for training and for research construction; nor, finally, on our year-by-year concern to assure support for all truly worthwhile research opportunities that currently are within our resources capability.

While these aspects continue to be important, even though not debated, it is becoming increasingly apparent that NIH programs can no longer be planned, discussed, or evaluated in their own terms, apart from other considerations. Granted that even in the past the matching of funds and programs to needs and opportunities could never be cut cleanly from surrounding circumstances, nevertheless, today, the impinging scientific, economic, and public policy elements exact a new order of attention. Certain of these matters are uppermost in my mind at this moment:

NIH and its programs have been influential in the development of a vigorous, and, I may say, highly productive, national enterprise in medical research. This activity has been characterized by high scientific quality, broadly ranging programs, and steady growth of both scientific and administrative capability. The very success of these programs, however, gives rise to proposals that this capability be directed toward a widening variety of national health or health-related problems. While many of these problems are undoubtedly urgent, and great public importance attaches to them, nevertheless they are apart from the essential role and function of the National Institutes of Health. In these circumstances we have tried hard to contribute to the solution of these problems within our program capabilities and limits. But we have resisted being districted by such problems, and particularly those aspects which clearly belong in other hands, or should be approached through mechanisms and arrangements more suited to the task than are ours. Only in this manner, I feel strongly, can we preserve and continue the integrity and thrust of our research and scientific efforts. Over the long run, I should add, these research and scientific efforts, with integrity preserved, may significantly change the circumstances out of which these other problems arise.

NEW CONCEPT OF PROGRAM DEVELOPMENT

At current levels of expenditure, NIH programs have moved well beyond the simple need to fill gaps in funding for broad research in the health sciences. Deficiencies of the past have been remedied, at least in terms of assured support for research ideas judged to be worthwhile. Clearly a new phase of program emphasis is called for—our main task today is to direct scientific efforts more purposefully—to assure that new perspectives are explored, and that advances in knowledge are quickly and effectively related to pursuit of our categorical objectives.

Pertinent to this, we are embarking for the first time upon a wholly new concept of program development, illustrated by the effort to mount research programs in the broad problems of child health and the phenomenons of human development. These activities are a significant departure from the heretofore categorical disease orientation of our programs. Furthermore, we are undertaking, on a major scale, the reducing of scientific knowledge emerging from the active research scene to application in the area of health practice. This is reflected, for example, in the efforts being directed toward the development of vaccines for the common respiratory infections as encompassed in the present program of the National Institute of Allergy and Infectious Diseases; and the acute leukemia therapy program now being mounted within the National Cancer Institute.

Thus our entire process of program planning and program development is being restudied now, to provide a more effective framework for these more complex programing tasks. There is need, of course, to be wary of risks inherent in attempting to prejudge the course of science; yet we must be alert to the manner in which our program activities do, and indeed should, influence the character and emphasis of research activity.

CONTINUING IMPERATIVES OF NIH PROGRAMS

Looking toward the future, I should like to emphasize these generalities as continuing imperatives for NIH programs:

Scientific comprehensiveness: Program support must be broad enough to comprehend all scientific and disciplinary areas relevant to total solution of health problems.

Maintaining vitality of biomedical research community: Programs must encourage a climate favorable to continuing growth of the community, as well as to maintenance of high scientific standards.

Maintenance of Intramural excellence: NIH began as, is now, and must continue to be, primarily a research institution of acknowledged excellence, imagination and drive.

Extramurally (there are two imperatives): NIH must assure a comprehensive range of research support programs and support mechanisms, sensitively directed to identifying and meeting current needs and opportunities of the biomedical research community.

Program policies and procedures must take into account and reconcile the divergent roles and responsibilities of a Federal science support agency, of grantee institutions, and individual scientists.

Building for future research capabilities: Our national research base must be kept expanding, so that our ability to satisfy health needs in the future will continue to be appropriate: to rising expectations of the people; to the dimensions of the health problem itself; and to the undoubted contribution medical research makes to national economic growth.

TRENDS IN FUTURE RESEARCH

In general, I anticipate these trends, and areas of emphasis in future research:

Behavorial sciences will be more important and productive.

More will be learned about normal mental processes, forming a better backdrop for studies ranging from mental retardation to intellectual excellence.

Processes of learning and cognition will be fruitfully investigated.

Sciences related to human development—particularly reproductive and genetic processes—will receive added emphasis.

Further advance will be made against diseases of virus origin—perhaps cancer.

Problems of environmental poisons and other hazards will receive greatly increased attention.

Epidemiological approaches will have added importance.

Additional concepts and technology based on physical science and mathematics will be extended to biology and medicine.

SUMMARY

Obviously, the basic political and economic realities that shape all Federal activities also set limits on health research. In recent years, the public consensus on NIH programs has been such that I know of no important instance where health research progress has been hobbled through lack of Federal support. But we recognize that health research is only one of several science areas dependent upon Federal support. We know, to, that limited Federal tax funds must stretch to meet many urgent needs of the people, among which science support has no proscriptive claim. We are content to rest our case for continued strong support for health research on the demonstrated ability of that research to meet health needs and health aspirations of the people.

BEHAVIORAL SCIENCES

Mr. FOGARTY. How do you define "behavioral science"?

You say behavioral sciences will be more important and productive.

Dr. SHANNON. Behavioral sciences compose a series of scientific areas that are concerned with explaining the basis of how an individual relates to other individuals within the same environment.

What is the basis for his emotional reactions to a wide variety of situations? And, in fact, what is the basis for the total community setting as it emerges in one type of culture or another? Why do individuals behave the way they do, whether as an individual alone, as an individual contained within a family group, as a family group contained in a community, or as a community contained in the Nation?

Behavioral sciences, as such, cover a very wide area—all the way from what one might call the hard science of social anthropology through an increasingly diffused range of concepts and analytical assessments relevant to man and his activities.

Mr. FOGARTY. If I gave that explanation in debate in the House there would not be a half a dozen people who would know what I had said.

Dr. SHANNON. I will ask Dr. Felix to give a more manageable definition of what are behavioral sciences.

Dr. FELIX. Mr. Chairman, I could not be more reasonable than that, because that was, I thought, very good. However, usually when we discuss the behavioral sciences, we talk about three which have specific bearing in our area here: psychology, sociology, and anthropology. There are other behavioral sciences, but we do not deal with them directly, such as economics, political science, areas of this kind, because this is also human behavior and the relation of one person to another. Does that answer your question?

Mr. FOGARTY. What is your definition of "psychology"?

Dr. FELIX. Psychology is the study of the mind—normal and abnormal.

Mr. FOGARTY. And sociology?

Dr. FELIX. Sociology is the study of individuals and their relations to other individuals in small and in large groups.

Mr. FOGARTY. What was the other one you mentioned?

Dr. FELIX. Anthropology.

Mr. FOGARTY. What is that?

Dr. FELIX. Anthropology is the study of the culture of people.

It is a study of the culture by which people live and which influences their behavior. For instance, one studies how the people on the island of Samoa live, and how they relate to each other, and what their customs are; this is anthropology.

Mr. FOGARTY. Mr. Denton can give you those answers. He has just been out there.

Mr. DENTON. Yes: I was in the islands.

Mr. FOGARTY. What is culture?

Dr. Felix. Culture is the mixture of special accomplishments, beliefs, and traditions which make up the background of a social group. For instance, there are fancy words such as the "taboos" and "sanctions" for characteristics that people incorporate into their society. For instance, in our culture—let me give you something rather extreme. In our culture, it is considered not right at all to eat human flesh. There are cultures in which this is considered all right, and even a religious function. For instance, in certain cultures, they will eat the heart of a brave chief and thereby take on some of his attributes of bravery. This is a cultural anthropological phenomenon of that society.

Mr. Lesinski. Mr. Chairman.

Mr. Fogarty. Yes.

Mr. Lesinski. Is not anthropology the study of mankind, his environments, and his social environments—background of the human race?

Dr. Felix. Yes, Mr. Lesinski. The borderline between sociology and anthropology gets fuzzy.

Mr. Lesinski. Anthropology is the study of our antecedents?

Dr. Felix. Yes; it can be that, too.

Mr. Lesinski. What does the word mean in Greek?

Dr. Felix. "Anthropos" means "man."

Dr. Shannon. Study of man.

Mr. Lesinski. Yes. In other words, the background of man.

Dr. Felix. Yes.

Mr. Lesinski. So, why a lot of words here?

Dr. Felix. Well, all right.

Mr. Lesinski. Thank you, Mr. Chairman.

Dr. Felix. I was just trying to be helpful; that is all.

1964 Reprograming

Mr. Fogarty. Now, Doctor, before we get into the 1965 budget, let us talk a little about 1964.

We approved your budget for 1964 with less change than Congress has made in any budget NIH has ever submitted, I think. Is that not about right?

Dr. Shannon. Yes, sir.

Mr. Fogarty. The main reason we did, we thought that the last budget submitted by President Kennedy was one of the most realistic budgets that we have had before us.

UNOBLIGATED BALANCES

Now, you have done a rather extensive job of reprograming and still estimate you will have unobligated balances at the end of the year in every institute.

Dr. Shannon. No, sir. In three institutes and one division, we we estimate we will have balances. Actually in some institutes, we will have shortages.

I can give you our best calculation of what those balances and shortages will be.

We figure in the National Institute of Child Health and Human Development, we may have balances as high as $5.8 million; in the Heart Institute, $4.7 million; in the Cancer Institute, $5.6 million; in biological standards, half a million.

Now, our calculations on program opportunities in the other institutes—these are primarily in the grant area—indicate a possible shortage of grant funds in general research and services of $3.4 million; in mental health, $1.1 million; in dental, $1.4 million; in arthritis, $4.5 million; in allergy, $3.6 million; and in neurology, $1.5 million. These add up to $15.5 million.

So currently in the overall budget there appears to be surpluses in four institutes and shortages in six; surpluses are $16.3 million, and $15.5 milllion in deficits.

Assuming that we will be able to reprogram to develop shortage areas contained in the six institutes, we would come within $1 million of the break-even point.

Mr. Fogarty. Now, those figures you just gave me do not correspond with the justifications that we have before us. Your justifications show you have a $437,000 balance in the child health——

Dr. Shannon. These figures have been developed in anticipation of the forthcoming round of councils, and are quite firm in terms of most of their estimates. It is on the basis of these figures that, on February 18, we sent a memorandum to our institutes—if you would like, I would like to make it a matter of record—indicating that no later than March 2 we would like a careful analysis of their programs, going into the last council meeting, which would serve as a basis for a recommenadtion.

I might say, Mr. Fogarty, that one of the problems, as I am sure you are very well aware, is with late appropriations and later apportionments. This type of information and this type of hardheaded analysis, which normally would take place in the fall, is deferred until about this time of year, when we know the personnel we have to work with, and we can explore our ability to expend the funds actually made available to us. Although figures differ from our original justification, these estimates are our best estimates of the situation in which we find ourselves today.

Mr. Fogarty. Have you discussed this with the Bureau of the Budget, about releasing some of these reserves?

Dr. Shannon. No; we have not, Mr. Fogarty. But, as in the past, we did not object to reserves on the understanding that at a later time in the program—when our needs could be backed up by hard data on research applications—we would have ability to request release of funds to satisfy such needs as could be demonstrated.

Of course there is no commitment to release those funds, but I have every hope that we can make a sufficiently strong case in the first couple of weeks in March, so that the funds will be released to satisfy these program needs.

SECRETARY'S LETTER

Mr. FOGARTY. Now, further on the reprograming, we shall put the Secretary's letter in the record.

(The letter referred to follows:)

JANUARY 6, 1964.

Hon. JOHN E. FOGARTY,
U.S. Senate,
Washington, D.C.

DEAR MR. CHAIRMAN: In connection with the development of budget plans for the current fiscal year the National Institutes of Health has made certain proposals for changes from the program presented to the Congress in the 1964 President's budget. These changes are necessary to meet provisions of the appropriation act for transferring funds to finance the new National Institute of Child Health and Human Development, to provide for new mandatory cost increases, to comply with policy changes, and to fund program needs not adequately identified at the time the budget was presented to the Congress.

We have carefully reviewed the plan that has been proposed by the National Institutes of Health and recommended by the Surgeon General. We believe that it will provide the best means of using available resources to meet the highest priority needs. We propose, therefore, to reflect these changes in the date to be shown as the 1964 base for the 1965 budget. The Department has no authority to transfer funds between appropriations. In our proposed usage of funds within each appropriation we believe that our recommended course of action is consistent with the expressed policies of the Congress and with our concern objective of pursuing the best possible program of medical research. We have especially been guided by the following:

1. The statement in the Senate report on our 1964 appropriation bill (pp. 32 and 33) emphasizing the need for additional funds for general research support grants. We are proposing to use an additional $5 million for this purpose.

2. The policy developed in conjunction with our hearings before the Fountain committee, whereby the Public Health Service no longer makes grants to profit-making organizations. Continuation of certain projects necessitates the transfer of about $1.5 million from grants to contracts.

3. Presidential policy to restrict employment, together with pertinent statements on this subject in the 1964 Senate and conference reports on the Labor-HEW appropriation bill. Our proposals contemplate no net increase in employment.

4. The statement by the chairman of the Labor-HEW Appropriations Subcommittee during floor discussion of the 1961 appropriation bill (Congressional Record, Aug. 25, 1960, p. 1786B): "I should like to emphasize that the specific amounts set forth in this table for the individual program elements comprising the several appropriations are not intended to be fixed or absolute levels of expenditure for the individual items. When changing operating circumstances require, I believe it important to leave it up to the good judgment of the program operators to make such adjustments in these amounts as is necessary in the interest of affective progress and prudent utilization of resources."

So that you will be fully advised of the recommended changes, my staff has developed a summary analysis which is enclosed for your review. In our considered judgment these are not departures from the basic purpose or intent of the provisions of each enacted appropriation. Rather they represent adjustments to make advantageous use of resources to carry out the intent of Congress and to permit each institute to pursue its program most efficiently.

Of the funds proposed to be reprogramed, $34 million represents transfers to the new National Institute of Child Health and Human Development in accordance with provisions in the appropriation act. Another $9.7 million will be used to fund previously unforseen program needs, to offset new mandatory costs for commissioned officer salary increases, to provide increased stipend allowances for predoctoral fellows, and to increase funds available for general research support grants. This $9.7 million will be financed from funds presently estimated to be in excess of the funds budgeted for regular research project grants.

We are aware of your sincere interest in the programs of the National Institutes of Health and of your past recognition of the need for flexibility in managing the finances of this large organization in order to accomplish maximum productivity within available resources. We sincerely trust you will be in agreement with the plans we have set forth. Should you have any questions, we shall be happy to arrange for any additional information you desire.

Sincerely,

Secretary.

Proposed Reprograming, Fiscal Year 1964

In developing 1964 operating plans for the National Institutes of Health it has been necessary to recommend a series of revisions from the budget plans presented to the Congress in the 1964 President's budget. These were necessary to meet provisions in the appropriation act for transferring funds to establish the new Institute of Child Health and Human Development, to provide for new mandatory cost increases, to comply with policy changes, and to fund program needs not adequately identified at the time the budget was presented to the Congress. The purposes for which reprograming has been proposed are summarized below.

I. TRANSFERS TO THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

In accordance with provisions of the 1964 appropriation act funds totaling $34 million have been proposed for transfer from the other appropriations of the National Institutes of Health as follows:

	Positions	Amount
General research and services	62	$9,646,000
National Cancer Institute		1,146,000
Mental health activities	46	6,914,000
National Heart Institute	3	4,981,000
National Institute of Dental Research		523,000
Arthritis and metabolic dsease activities	4	5,980,000
Allergy and infectious disease activities		1,606,000
Neurology and blindness activities	12	3,204,000
Total	127	4,000,000

The amounts transferred from each appropriation bear a relationship to the research grants, fellowships, and training grant programs identified for transfer to the new Institute. They do, however, provide for some allowance for program expansion in these activities as well as for administrative costs. A total of 127 positions from these organizations has been made available to the new Institute in these transfers.

II. TRANSFERS DUE TO POLICY CHANGE

In connection with major policy and procedure changes affecting the administration of the research grants programs of the Public Health Service, a decision was made to discontinue the practice of awarding research grants to profit-making organizations. Projects conducted by these organizations will in the future be financed through contractual arrangements. For those Institutes and Divisions which wished to continue projects in profit-making organizations which were presently being funded through grants, it is necessary to provide funds in an appropriate activity to be used for contracts. Since the projects are for the same general purpose as those funded through grants, it is appropriate to transfer resources from the research grant activity. Transfers from research grants to the activity collaborative studies, for the purpose explained above, have been recommended for the following appropriations:

General research and services:	
Division of Research, facilities and resources	$315,000
Institutes of General Medical Sciences	667,000
National Institute of Dental Research	565,000
Total	1,547,000

III. TRANSFER OF FUNCTION

Late in fiscal year 1963 it was determined to be in the best interests of the Service to strengthen the grant policy operations of the Public Health Service by establishing in the Office of the Surgeon General an Office of Grants Policy. This involved the transfer of responsibility from the Bureaus to the Office of the Surgeon General under provisions of section 202 of the Public Health Service Act. Section 508 of the act authorizes the transfer of funds necessary to carry out the purpose of any reorganization under section 202. The share of 1964 operating year costs for the Office of Grants Policy designated for the National Institutes of Health was $90,000 and seven positions. Positions and funds are being transferred from the following sources:

	Positions	Amount
General research and services	2	$17,000
National Cancer Institute	1	15,000
Mental health activities	1	15,000
National Heart Institute	1	15,000
Neurology and blindness activities	2	28,000
Total, NIH	7	90,000
Bureau of State Services	2	14,000
Total, grants policy staff	9	104,000

IV. REASSIGNMENT OF UNPROGRAMED FUNDS

In the process of evaluating the 1964 operating plans of the National Institutes of Health following the appropriation, it was estimated that there was approximately $35.7 million which was budgeted for regular research projects and for certain training programs that will not be required for these purposes. These anticipated balances were largely in the regular research grants activity in which projections based on 1963 operating experience indicated that the 1964 requirements would probably be about $30.8 million less than the amount designated for this purpose in the 1964 President's budget. There have been, however, certain needs recently identified which were either unanticipated at the time the President's budget was prepared or were underestimated at that time. The reassignment of unprogramed funds would provide the opportunity to meet these unforeseen needs without requiring a supplemental appropriation of funds for 1964. The total amount of $9,675,000 proposed for reprograming would be derived from anticipated balances in each of several appropriation accounts.

General research and services	$912,000
Child health and human development	388,000
National Cancer Institute	921,000
Mental health activities	833,000
National Heart Institute	1,695,000
National Institute of Dental Research	231,000
Arthritis and metabolic disease activities	2,064,000
Allergy and infectious disease activities	772,000
Neurology and blindness activities	1,859,000
Total	9,675,000

These funds would be used for mandatory costs and other identified needs. The major share of the funds would be reprogramed within the appropriations, although $295,000 of this amount would be reflected as an increase in the reimbursement to the management fund as explained below. The following is a summary of the purposes for which reprograming of balances is proposed

A. Commissioned officer salary increases

Reprogramed within appropriations:

General research and services	$28,000
Child health and human development	11,000
National Cancer Institute	201,000
Mental health activities	211,000
National Heart Institute	185,000
National Institute of Dental Research	84,000
Arthritis and metabolic disease activities	134,000
Allergy and infectious disease activities	148,000
Neurology and blindness activities	88,000
Total	1,090,000

B. Research fellowships, increased stipend rate

As a result of recent nationwide studies, the Budget Bureau has approved an increase in the stipend rates for predoctoral fellowships which will begin in fiscal year 1965. This policy affects all Federal agencies granting such awards and includes provisions for awards made from 1964 funds which will be in support of fellowships to be active in 1965. The National Institute of General Medical Sciences and National Institute of Mental Health will each require $108,000 to supplement their 1964 fellowship funds in 1964 for this purpose. In both cases the funds would be made available from anticipated balances of research grant funds in their appropriations.

C. General research support grants

Subsequent to presentation of the 1964 President's budget, it has become apparent that funds in excess of the $30 million programed for general research support grants will be required to maintain continuing stabilized support to those institutions receiving awards in 1963 and to grant awards to other institutions which have become eligible more recently. This need was recognized by the Senate in their report on the 1964 appropriation bill (pages 32 and 33). An additional $5 million is proposed to be used for general research support grants rather than for research projects grants, as authorized by section 301(d) of the Public Health Service Act.

General research and services	$776,000
Child health and human development	377,000
National Cancer Institute	720,000
Mental health activities	350,000
National Heart Institute	431,000
National Institute of Dental Research	135,000
Arthritis and metabolic disease activities	1,007,000
Allergy and infectious disease activities	566,000
Neurology and blindness activities	638,000
Total	5,000,000

D. Transfers to meet direct operations requirements

Identified additional direct operations requirements for which reprograming within the appropriations is proposed, total $3,369,000. The appropriations in which the transfers would be accomplished are:

Mental health activities	$164,000
National Heart Institute	1,079,000
National Institute of Dental Research	12,000
Arthritis and metabolic disease activities	923,000
Allergy and infectious disease activities	58,000
Neurology and blindness activities	1,133,000
Total	3,369,000

These funds will be directed to four direct operations activities: (1) collaborative studies, $2,548,000; (2) professional and technical assistance, $123,000; (3) review and approval, $17,000; and (4) research, $681,000. The latter includes $216,000 for increased reimbursement to the management fund to meet mandatory costs of wage rate salary increases which became effective after the President's 1964 budget was presented to the Congress. An additional $43,000 for this purpose is available from the direct operating funds of the Child Health Institute and the National Cancer Institute.

The purposes for which these funds have been requested are summarized below:

1. *Collaborative studies, $2,548,000.*

National Heart Institute, $575,000.—$75,000 of this amount is required to support the unanticipated extension of work of the Surgeon General's Advisory Committee on Smoking. Additional funds were not planned for this purpose in the budget since it was then contemplated that work of the Committee would be concluded in 1963.

Five hundred thousand dollars is required for contracts for the production of urokinase (an agent for dissolving blood clots), antihemophilic globulin, and erythropoietin (an agent important in regulating red blood cell production). These substances are essential to continue progress in research supported through grants of the Institute. It has been found necessary to arrange for their production through profitmaking pharmaceutical houses, thus requiring funds for contractual arrangements.

Arthritis and metabolic disease activities, $873,000.—These funds will be for the support of operations and services for which it has been determined to be more prudent to fund through contractual arrangements rather than grants; $780,000 will support two center operations, one for pituitary gland collection and distribution and hormone production, the other a steroid reference collection; $93,000 will be used to contract for abstracting services necessary for furthering advancement of scientific communications.

Neurology and blindness activities, $1,100,000.—Of this total $500,000 is to support, through a contract, a study center for research and research communications in Parkinson's disease and allied disorders. The contract is a preferred method of funding for this kind of activity. The additional $600,000 is required for data processing costs, collection, and storage of sera and other support requirements for the perinatal research collaborative program. Materials and information are becoming available more rapidly than anticipated and these funds are necessary to take advantage of the opportunities presented.

2. *Professional and technical assistance, $123,000*

These are funds of the Mental Health Institute required for projects in alcoholism, juvenile delinquency, and mental retardation which were not anticipated at the time the 1964 President's budget was developed.

3. *Review and approval, $17,000*

An additional $17,000 is required by the Institute of Allergy and Infectious Diseases for costs of a recently activated data processing project needed to improve grants management operations of the Institute.

4. *Research, $681,000*

Of this amount $261,000 is being used to offset mandatory costs of wage rate salary increases. The balance of $465,000 is required by the National Heart Institute to meet unanticipated research needs for equipment, research animals, human blood, and radioisotopically labeled materials ($375,000), and renovation costs to provide an anaerobic (oxygen-free) laboratory ($90,000).

V. REDISTRIBUTION OF STAFFING ALLOWANCES

Critical staffing needs beyond the allowances provided in the 1964 President's budget for some NIH organizations were identified early in this fiscal year. In view of vigorous efforts of the administration to check the overall expansion of Federal employment, it has not been practical to seek authorizations which would increase employment within the Department above planned levels for 1964. Consequently, to overcome inadequate staffing availability in various programs, it is essential to look to the redistribution of staffing allowances within total ceiling for groups of operational units. Such flexibility is considered essential to meet unanticipated requirements. Within this framework the National Institutes of Health has proposed the redistribution of 81 positions between major operating organizations. While these redistributions do not involve transfers of funds between appropriations, they do require a reprograming of funds between grants activities and direct operations activities. The adjustments also involve a net increase of $76,000 in reimbursement to the management fund.

Sources of employment ceiling

	Position reduction	Total fund adjustment	Transfer from direct to grants	Increased reimbursement to management fund	Transfers within management fund
Biologics standards	3	$13,000		$13,000	
Cancer	25	112,000	$90,000	22,000	
Heart	12	53,000	43,000	10.000	
Neurology	36	160,000	129,000	31,000	
Management fund, internal adjustments	5	50,000			$50,000
Totals	81	388,000	262,000	76,000	50,000

Recipients of employment ceilings

	Position increase	Total fund adjustment	Transfer from grants to direct	Increased reimbursement to management fund	Transfers within management fund
Child health	16	$91,000	$91,000		
Mental health	6	36,000	36,000		
DRFR [1]	25	135,000	135,000		
Management fund	[2] 34	126,000		$76.000	$50,000
Totals	81	388,000	262,000	76,000	50,000

[1] Division of Research Facilities and Resources.
[2] Includes 5 from internal management fund adjustments.

The purpose for which increased staffing is required for each of these organizations is summarized below:

A. Child health and human development

Research, five positions, $28,000.—To permit early development of direct research operation in perinatal physiology. This increase will provide a total staff of 15 for the NICHD research operation.

Collaborative studies, $23,000.—This amount is required for contracts to study and identify needs and opportunities as a basis for evolving a comprehensive program of child health and human development.

Program direction, 11 positions, $40,000.—Staff ceilings required to recruit program specialists and supporting staff required for program development and program direction. Four positions are included for new program for construction of mental retardation facilities.

B. Mental health

Professional and technical assistance, six positions, $36,000.—This staff is required for assisting States in connection with the new program for grants for the construction of community mental health centers.

C. Division of research facilities and resources

Review and approval, 13 positions, $91,000.—All positions are required for engineers and program specialists to review applications for construction grants, to develop criteria and policies, and to make site inspections and review of projects in progress and upon completion of construction. Eight positions are required to meet backlogs related to continuing programs and five are required in connection with the new program for construction of mental retardation facilities. An additional 12 positions and $44,000 are needed for program direction.

D. Management fund activities

Program direction, seven positions, $42,000.—These positions are required to meet commitments for developing a sound program of scientific communications and for providing more adequate program and management planning resources in the Office of the Director.

Office of Administrative Management, 17 positions, $84,000.—These positions are essential to cope with mounting backlogs in the financial management operation. Presently authorized staff is inadequate to keep pace with the growing volume of business generated through the activation of new organizations and the expansion of continuing programs, increased demands on budget operations, and grant payment and audit activities.

Division of Research Services, 10 positions.—These 10 positions transferred from the Institutes and 6 to be made available from within the Division will provide a total increase of 16 positions for advancement of the program in computer sciences and technology. This program is an essential support element for the progress of research in the biomedical sciences. Adequate funding resources are available to the program to support these positions.

Mr. FOGARTY. Now I shall ask you for the record to tell us just why you felt this was proper and necessary for the most efficient and beneficial expenditure of these funds. This is a bit controversial, so take your time.

Dr. SHANNON. Well, Mr. Fogarty, in putting the Secretary's letter in, are you going to put in his attachments? Because this really takes up item by item——

Mr. FOGARTY. Yes, we shall put the whole thing in.

Dr. SHANNON. Well, I will answer some of the questions, Mr. Fogarty, but I will have to have some help from Mr. Kelly and some of the others.

There are two categories of transfer that are proposed in the reprograming of these dollars. The first, I would say, is in the area of administrative concern to satisfy such anticipated needs as pay raises and the like. The reprograming of dollars to satisfy this is settled in discussion between Mr. Kelly's office and the Bureau of the Budget, on the one hand, and Mr. Kelly's office and my office on the other.

The reprograming that we have proposed was, I think, well within the intent of the Congress in making the appropriation available to us, and I would say particularly in accord with your own floor statement on previous years, which is quoted by the Secretary in his letter.

CONDITIONS CHANGED AFTER BUDGET SUBMISSION

This is the situation we found ourselves facing last fall: Our best judgment in the preceding fall—1962—was the basis of the Presidential budget request. Subsequent to submitting that request, we had gained two new institutes, plus quite broad legislative programs in both mental health and mental retardation. Also subsequent to our budget request, we appointed a Director of the new Institute of Child Health and Human Development and undertook in the spring and summer a very careful survey of how we could respond best to the impact of quite broad new programs that were actually being undertaken. These programs had an impact across the board on training opportunities, on research, and on the needs for resources.

It was quite apparent by as early as June or July, that if we were to follow the detail of the original budget submission, it would be impossible to produce the most efficient program overall. Therefore, we undertook discussions first with the Department and later with the Director of the Bureau of the Budget, relative to movement of some funds.

Some movement of funds was needed to satisfy simple administrative changes, such as moving profitmaking concerns from the grant area to the contract area. Other movements of funds related to certain items previously covered by research grants that might better be done under a collaborative arrangement, which appears in a different place in the budget, and in general is handled by contract rather than grant.

I think that if one goes over the transfers item by item, one would find that in no single instance, up to the present time, has there been any diversion from the primary intent of the appropriation. The diversion has only been in the mechanics of how we expend the money in order to achieve the purpose.

Let me explain further a rather special case pertinent to the Cancer Institute only.

REPROGRAMING FOR THE CANCER INSTITUTE

The Cancer Institute has been arranging for more and more of its training programs to be taken up by the National Institute of General Medical Sciences. In going over the appropriation that would probably be available, I suspected—late last summer and again last fall—that it would be advisable to curtail the amount of money spent for training in the Cancer Institute, and to utilize some of the funds for special purpose programs that had received very broad support in both the House and the Senate committees. I am referring particularly to efforts in the area of carcinogenesis, either chemical or virological and in broad studies of its biological base.

At that time, it was the best judgment of the Department that this constituted a sufficient change in purpose, that it probably was not allowable. However, we propose to discuss these points further because we feel that in the aggregate we would not be modifying the program intent as contained in the congressional budgets.

I think what we are doing is using the experience we now have, some 18 months after our original program was proposed, in order to give to the Congress the best program that we can within the appropriation limits that were set, and in general accord with the reports in both the House and the Senate as to those areas they wish emphasized.

So that I think that any reprograming of dollars in our program can be defended as consistent with original program purpose.

DIRECT RESEARCH FOR NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. Seggel points out there is another area of need that was not anticipated in the 1964 budget. The 1964 budget did not provide for direct research costs of the National Institute of Child Health and Human Development. In the reprograming of dollars, we have provided for a small beginning of the direct research program in this area. Again I would point out that at the time the program for Child Health and Human Development was written into our budget request, the

Institute was not fully established. We did not have a Director. We had no employees to develop the program. So that the program that has evolved now is within the pattern we defined before this committee, but the mechanics by which the program has evolved have been modified slightly. Here, too, I really do not believe, sir, that there is contained in any of our requests for reprograming any modification of the basic intent of this committee or any modification of the basic intent of the Senate committee.

Now I would turn to Mr. Kelly for those elements of reprograming in dollars that involve general departmental policy on problems that are generated from a reaction to change in pay scales.

REPROGRAMING BECAUSE OF CHANGES IN PAY SCALES

Mr. FOGARTY. Mr. Kelly.

Mr. KELLY. At the time we appeared before you for the deficiency item, Mr. Chairman, I brought to your attention that we had both the wage board increase and pay increase for uniformed personnel. Part of this was absorbed; the part that affected the National Institutes of Health was substantially absorbed within the appropriation for NIH. Then with respect to the rest of the Public Health Service, we proposed to you the transfer of $3,350,000 out of the National Heart Institute reserve to pay the cost of these increases throughout the Public Health Service. That was out of a total reserve of $7.8 million. And I pointed out that even if we were in error as to the number of approvable projects that would be received, we estimated a substantial margin of error to cover this before the year was over.

DEPARTMENT'S NEW REGULATIONS ON REPROGRAMING

Just to underscore that, Dr. Shannon has said that we are concerned with the problem that has arisen with respect to reprograming. The Secretary has recently issued a budget circular dealing with this in order to make sure that our handling of it is as we intended, as we have told the committee.

It has been our view that the Congress wants us to carry out the programs of the Department in such a way as to get the best utilization of the funds for the furtherance of our program as possible, but not to initiate new activities or new endeavors without consultation with the Department.

When we make what we consider to be a significant change in the program activity, which we have testified to, we call it to the committee's attention by letter, and we endeavor to do so in a timely way, so that if the committee reacts adversely to our proposal, it can be made known to us in advance of any action taking place.

But in the National Institutes of Health, where you have very large sums of money divided up by Institutes, and then within each Institute, leading to a whole series of categories, like regular grants and special grant areas, and training grant areas, and direct operations, and each of these subdivided. It would be a straitjacket, to try to stay within each of these. But it has been our plan to call to your attention significant deviations from them. In two instances in this reprograming letter that we have sent to you, the reports of the

Appropriations Committees were at least partially instrumental in bringing about the reprograming.

RESPONSE TO SENATE COMMITTEE

The Senate committee report was critical of the fact we had not utilized, to the extent contemplated in the original legislation, the authority to make general support grants to institutions involved in continuation of research.

When we reexamined the availability of funds in the light of last year's experience and what the cost of continuation grants were and the probable number of approvable new grants that would be received, it was apparent that we could increase general research support grants within the total available appropriations, and we have proposed to you that we increase them by $5 million over the budget. We feel that this was responsive to the Senate committee report.

Similarly, the Senate committee report commented on the decreased estimate in training and fellowship area in the Cancer Institute, and recommended a greater amount of work in the collaborative contract field. And then at the time we testified, we told you that we were changing our policy on utilizing contracts, rather than grants in doing business with profitmaking institutions. This is another significant area in the reprograming letter we submitted to you.

Mr. Fogarty. Did you ever get any answer to any of these letters?

Mr. Kelly. No, sir. But I do not feel that it is appropriate for us to take the position that we require an answer. I think that it is appropriate for us to bring them to your attention early enough that if you want to respond, you can, and if you do not respond, we assume the full responsibility for the action we take and allow a reasonable period of time to elapse, and then proceed to carry out the plan that we have submitted to you.

Mr. Fogarty. Well, my own position is that I am not overly concerned about this kind of reprograming, but there are members of the committee that are. That is why I raised the question.

I realize that some of the blame can be placed on the Congress, because even though we passed the bill in the House at the end of April, it did not clear the Congress until about the first week in October. This year it is going to be another story. We hope to have it through the House April 14, and the way the Senate is going now, I would guess that they would pass it very soon after that unless they are tied up on civil rights. We hope that for the first time in many years, you will have your appropriation before the beginning of the fiscal year.

OVERALL PATTERN OF 1965 BUDGET

Now, looking through the justifications for 1965, there seems to be a general pattern for all institutes that there are small dollar increases for research grants, but it is almost all for continuation of going projects and none for an increase in new projects; that there is practically no increase in the programs for fellowships and training; and that the increases for direct research are insignificant. Is this a fair analysis?

Dr. Shannon. I would like to take them up individually. If you will read one at a time, Mr. Fogarty—some of that is correct, and some is not. What was the first one?

Mr. Fogarty. You can pick it apart if you want to. This is an overall look, and this is the conclusion I came up with.

Dr. Shannon. In general, for grants, there is little change from last year.

Mr. Fogarty. That is what I said.

Dr. Shannon. There is some dollar increase in training grants.

Mr. Fogarty. I said no increase in new projects.

Dr. Shannon. This is generally correct, sir, with respect to research grants.

Mr. Fogarty. And no increase for the program for fellowship and training.

Dr. Shannon. Except for training grants in two institutes; namely, the National Institute of General Medical Sciences, $1.5 million; and the National Institute of Mental Health, which was approximately $8 million. The others had no increases of substance.

Mr. Fogarty. But in total, it is just about the same, is it not?

Dr. Shannon. $11.3 million increase, sir.

Mr. Fogarty. In total?

Dr. Shannon. In total.

Mr. Seggel. That is for training grants, sir. Approximately $700,000 of the total increase of some $12 million is for fellowships.

Dr. Shannon. About $8 million of the total increase is for mental health service training, and the remaining $3.3 million of the training grant increase is divided among a number of institutes; $1.5 million going to the National Institute of General Medical Sciences.

Mr. Fogarty. How much of that total would be for increased costs?

Mr. Seggel. There is an amount of $951,000 within the total estimate for increased stipend rates for fellowships; I do not have computations relating to training grants.

Mr. Fogarty. I mean all increased costs now.

Dr. Shannon. Well, the $8 million is——

Mr. Fogarty. With those two exceptions all of it would be for increased costs, I would guess.

What I said at the beginning is just about right, isn't it?

Mr. Seggel. Except there is an $8 million increase in mental health, which should provide some program expansion.

Mr. Fogarty. Overall, it looks like a standstill budget to me. In some places you are falling behind instead of keeping up with the going programs.

I think it is the sense of Congress that we wish to keep up the momentum that has been gained in the past few years, maybe not as rapidly as 2 or 3 recent years when we increased the budget quite substantially, but not to stand still, because if we stand still we are really going behind, as far as I am concerned.

Dr. Shannon. I can give you some specific data.

On the fellowships, there are increases for predoctoral stipends and for the career development and career award programs, offset by decreases in postdoctoral and special fellowships.

So that in the aggregate, the fellowship program does in fact stay at about the same level.

In training, the increase, $168 to $180 million, will allow an advance in mental health programs, and in general medical sciences programs also. The remainder will stay roughly at present levels.

Mr. FOGARTY. If you leave out the Mental Health Institute there is almost no change?

Dr. SHANNON. Yes.

Mr. FOGARTY. That is what I call falling behind.

CRITERIA FOR ARRIVING AT 1965 BUDGET

Was there any overall criteria or guidelines used in arriving at these requests for 1965?

Mr. KELLY. The answer to that is "Yes," sir. At the beginning of the budget cycle, the Secretary issued a series of policy assumptions which governed the development of the budget. In the specific areas you are talking to, one of the assumptions was that, with minor exceptions, that the research grant program should be supported at levels which would provide for approximately the same number of new projects in 1965 as we were able to support or as were required, as were available for support in 1964, plus the estimated costs of continuations and supplementals with respect to ongoing programs.

Mr. FOGARTY. Was he told to issue this ultimatum?

Mr. KELLY. It was not an ultimatum; in order to prepare any kind of total overall budget, you have to prepare a series of basic assumptions. This is one of them.

It stemmed from an identification of the concept of the President's program of having reduced taxes, and thus, for a period of time, pending getting the full effect of them, there would be deficit financing. And it also stemmed from the realization of the tremendous increases that had already been recommended for the areas in the Department of Health, Education, and Welfare, in the President's program, particularly the new legislation, much of which was enacted in the last session of Congress.

Mr. FOGARTY. I think we will be able to show he was entirely wrong. By increasing this budget, we perhaps could have saved the Federal Government a great deal of money. I think that was demonstrated very well in the tuberculosis area last week. If there was ever a case of false economy, it showed up last week in several items that were heard here.

In issuing such an ultimatum, the Secretary in effect said to every Institute Director "We will allow you to carry on at the same rate as 1964, but we won't give you one dime for any increase in new projects over the 1964 rate, no matter how good they are." That is my analysis of what the Secretary said to them. This is shutting the program right down. Is that what it was mean to do, shut it off?

Mr. KELLY. No, sir; as a matter of fact——

Mr. FOGARTY. They did not allow any increase in new projects?

Mr. KELLY. Such an arrangement does result in substantial expansion.

Mr. FOGARTY. This is a change. This action does not go along with the President's message on health. I read that message two or three times. All the newspaper publicity I saw indicates others understood it the same as I did; that we were going to do a better job in this area than we have ever done before.

SHIFTING ACTIVITIES TO INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

At the time of our hearings last year, there was a little doubt, it seemed to me, regarding the guidelines for shifting activities from the established Institutes to the new Institute of Child Health and Human Development. Will you tell us what these guidelines were and what programs were transferred? So far as you can tell now, have all the transfers been made, or have some been deferred until next year's budget?

Dr. SHANNON. All of the transfers, Mr. Fogarty, not only in terms of the aggregate dollar values but also in categories of grants, were completed last year.

Now, in developing the program, however, it was decided to limit the initial phase to a series of areas that are considered critical and to place particular emphasis on getting these underway. These had to do with mental retardation, with maturity, with biology of reproduction, and with aging.

There is no doubt that as the years go on, as the program develops, there will be further interchange between this new Institute and the others. But this will be of a minor nature, save in one particular area, and that is in the area of aging. For direct operations, aging is now carried in the Heart Institute budget. You may recall, sir, that construction of a gerontology research facility in Baltimore was authorized, to be funded by the Federal Government, and to be used primarily as a branch of the Heart Institute. This facility also provides space for invited investigators, the scientists of the Baltimore metropolitan area, Johns Hopkins, and the University of Maryland.

It is our judgment that with the new Institute Director unaccustomed to the complexities of building programs within the Federal Government, it would be wise to leave that direct operation within the Heart Institute until the program is further along, and the building has been built. At a later date, transfers can be worked out. This is a single package that can be handled as a single package, and we felt it made good administrative sense to leave it within a strongly organized administrative framework. So, save for that, our transfers have been long since acomplished, sir.

FISCAL CONTROLS ON GRANTS

Mr. FOGARTY. We talked to the Surgeon General earlier about the new regulations; the fiscal controls on grants.

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. Is there anything else you would like to add? You were here that day.

Dr. SHANNON. Yes, sir. First, let me start my comment by saying some of the problems we found ourselves in in the area of grants management stemmed from the fact that there are contrary situations concerning contracts. There is no fixed body of law that governs the grant mechanism as compared to the fixed body of law that governs the contract instrument.

As you know, we were criticized by one of the House committees on grants management policies that they thought were not to the best interest of the program. They questioned whether our administrative arrangements were sufficiently prudent, and whether our superior system of analysis of program requests was matched by adequate followthrough on the performance of the research. Other points involved the relationship between the university on the one hand, and Federal Government on the other, including the need for continuing overview of the substance of the work that was accomplished by the program. There was concern that the official relationship of the granting agency to the grantee should not cease at the time funds were made available, and were not limited simply to productivity of science.

We have done much rethinking about what the normal relationship should be between the grantee institution, the scientist, and the Federal Government, and about what normal relationship should obtain, in order to assure on the one hand vigorous, independent research on the part of the scientists, and mature and careful expenditure of public funds on the part of the granting agency.

Out of this rethinking came a series of rules and regulations that were codified and were in fact quite restrictive, as compared to the set of circumstances that had obtained heretofore. But, nonetheless, it was incumbent upon us to specify quite clearly the authorities within the grantee institution to move funds from one budget category to another, to change the direction of the program or the type of accounting, and to require permission from the Public Health Service, if such changes were substantive or extensive.

Mr. Fogarty. You mean you asked them to stop doing some of the things you asked Congress authority to do yourself?

Dr. Shannon. In fact, yes. It is precisely that.

If they wish to reprogram dollars, what they do now is to call this to our attention in precisely the way we call it to your attention; and to give us an ample opportunity to object to it, when we feel a change is not in the best interest of the program, or is contrary to the intent of the research grants.

So that their relationship to us is not too different from our relationship to you.

Mr. Fogarty. That is all there is to it, they just write this letter to you and say, "We want to change directions here"?

Dr. Shannon. Yes, sir.

Mr. Fogarty. Unless you respond, they go ahead?

Dr. Shannon. We take a positive action in all cases, because this involves an audited procedure. We say "yes" or "no." Quite frankly, we usually say "yes."

Mr. Fogarty. Is it possible to estimate about how much additional annual expense there is to the Public Health Service and to the schools and other grantees as a result of the tightened-up fiscal controls?

Dr. Shannon. Mr. Fogarty, this is impossible. All I can say is that it is substantial, both in time and effort. We have tried to find some way of estimating the costs, but so far have been unable to find any.

Mr. Fogarty. But it is substantial?

Dr. Shannon. It is substantial; yes, sir.

Mr. Fogarty. That is about all you can say?

Dr. Shannon. That is all I can say.

PLANS FOR DECENTRALIZING ACTIVITIES AT BETHESDA

Mr. FOGARTY. Now, there has been some discussion during the last few years of whether or not it would be desirable to decentralize some of the activities now at Bethesda. What have you done, if anything, and what are your plans for the future?

Dr. SHANNON. We have undertaken two studies. The first was to lead to the setting up of an office in a metropolitan area—as a matter of fact, Boston was selected as the trial area—in order to determine what functions could be discharged on a peripheral, as opposed to a central, base. This study was to start the 1st of April, and would have involved the assignment of about 10 people and, if successful, the management aspects of the branch would then find application in regional offices across the country, perhaps.

Many management decisions that were purely of a fiscal or business nature, many informational activities, that could be done peripherally rather than centrally, were to be handled in this office.

Mr. FOGARTY. Are you going to start this study?

Dr. SHANNON. No, sir. We have temporarily delayed it for two reasons: It is our best judgment that this will increase substantially the cost of grants administration. And while it may improve quality, there is no doubt that costs will increase both in terms of the number of people engaged, and the dollars necessary to support them. So that we have put this aside for the moment, until we pursue the second study that will go forward; namely, to determine the extent to which some of the management decisions we make now in Bethesda can be transferred to grantee universities.

Now, these decisions have to do with the purchase of equipment, the movement of dollars from one category to another, and an estimate of the impact of any change in the program.

Our discussions up to the present time indicate that it probably will be possible in most scientific environments to establish within the institution a scientific group that can assess for us the needs for such program changes, and can document the decisionmaking process in an advisory fashion, so that we can be concerned with the characteristics of the decisionmaking process rather than the individual decisions themselves.

This would, in the coming months, go on trial in as many as 12 institutions, most of these selected from the Northeast and Washington metropolitan area, as a convenience to us, to assure easy accessibility.

Now, if this works out as we expect it will, this will substantially reduce our workload in Bethesda, and it then will be possible to go back to the first study and find out the extent to which an office in the field will facilitate this transfer of authority to the university.

PROJECTS RIDICULED IN PRESS

Mr. FOGARTY. Every year there are some of your projects that are ridiculed in the press and elsewhere by people who know no more about them than the title. I am sure most of these that get much publicity come to your attention.

Will you place in the record the ones that have been ridiculed during the last 2 or 3 years, and what each project is really about, and the accomplishments?

Dr. SHANNON. This we will be glad to do, sir.

(The requested information follows:)

SPECIAL REPORT: GRANTS SUBJECT TO RIDICULE

During the past year, there has been a striking decrease in criticism of PHS research grants. This undoubtedly reflects the confidence expressed by the committee in the administration of the grants, and perhaps even more, the part the committee members have played in informing and educating the Congress and the American public as to the problems and distinctive nature as well as the benefits of medical research.

In previous years, a small number of Public Health Service research project grants were ridiculed. A list of these, and an explanation of the exact nature of the research and the benefits to the public health have emerged and might be expected from it, follow:

COMPREHENSIVE BEHAVIORAL STUDIES OF MONKEYS

Dr. Harry Harlow, one of this country's most noted experimental psychologists, has conducted numerous investigations on the social behavior of primates. Among these the problem of the effects of mother-infant relationship on the future social development of the animal has occupied a central position. He has shown that the experimental manipulation of the physical characteristics of "the mother" (through substitution of surrogate, frame-mothers) can influence social responses of the infant monkey to other infants, as well as its perceptual and learning capacities. Further, these influences are maintained over a long period of time and affect the maternal behavior of the adult female when she has infants of her own.

He has also shown the importance of relationships with other infant monkeys. One of his most striking findings has been that a period of total isolation for the first 6 months of life renders an animal permanently inadequate to develop normal behavior in later life.

Beyond these studies, Dr. Harlow and associates are conducting a variety of investigations on the developmental aspects of learning and problem solving in monkeys, on motivation, on the development of visual exploration and curiosity, on the effects of cortical lesions on the subsequent development of behavior, on the effect of induced phenylketonuria (a disorder which produces mental deficiency in humans) and others. He is studying the nature of behavioral changes resulting from metabolic disorders.

Dr. Harlow's work has important implications for a deeper understanding of human behavior. For example, there is a general argeement among mental-health practitioners that the nature of the mother-child relationship is critical in the development of a child's ability to establish healthy and satisfying interpersonal relationships, and there is some reason to believe it affects the development of intellectual function also. For ethical reasons, such investigations often cannot be undertaken on human subjects. The research is an essential supplement to research performed directly with human subjects and paves the way for new and better human research.

NUTRITIONAL TEAMS ABROAD

The nutritional teams that have gone abroad have been sent by the Interdepartmental Committee on Nutrition for National Defense which was organized in 1955 and is formed by representatives from the Departments of State; Health, Education, and Welfare; Defense; Agriculture; the Agency for International Development; and the Atomic Energy Commission. The Secretariat of the ICNND is located on the campus of the National Institutes of Health and operates administratively through the National Institute of Arthritis and Metabolic Diseases.

The international responsibilities of this Institute in nutrition research were incorporated into the Institute at its formation and have for their basic purpose the accumulation of fundamental scientific data directly related to our understanding of diseases of importance to the health of the people of the United States.

Following an official request from the country concerned, transmitted through State Department channels, the ICNND and the government of the host country organize a team of nutrition scientists from the laboratories and universities of both countries (usually about 15 Americans and 2 to 3 times this number from the host country). The team then undertakes an extensive survey of each aspect of nutrition throughout the country, from which results a detailed scientific report both in English and the national language, with recommendations centering about self-help programs designed to improve the nutritional status of the local population. Every effort is made to coordinate recommendations with existing and envisioned programs of the host country and the United States.

The activities and accomplishments of the ICNND were reported to this committee during hearings on fiscal year 1963 appropriations for the National Institute of Arthritis and Metabolic Diseases and were published in the hearings. Since that time, four additional surveys have been made, one each in Uruguay, Jordan, Bolivia, and Malaya.

STUDIES OF BODY TEMPERATURE REGULATING MECHANISMS

As previously reported, this study, which is being carried out by Dr. James D. Hardy, director of the John B. Pierce Foundation Laboratory, New Haven, Conn., under PHS Grant No. B–3826, is based on the fact that the regulation of body temperature is one of the most important homeostatic mechanisms of warmblooded animals. In the human, prolonged body temperatures above 106° F. are incompatible with life. A change in body temperature is one of the prominent features of many infectious diseases. Recently, the use of lowered body temperature during anesthesia has proven a valuable aid to surgery. An exact knowledge of the temperature-regulating mechanism is essential to further refinement of this technique.

Newly developed techniques, especially those involving the use of microelectrodes in the brain, now make it possible for the first time to record the activity of nerve cells within the brain that are involved in the temperature regulating mechanisms. In addition, refinements of the methods for measuring heat exchange now make possible an exact correlation between the regulatory function being performed and the activity of the nervous system responsible.

There is some evidence that the hypothalamic area of the brain may be the part of the nervous system which controls body temperature. However, this has not been satisfactorily substantiated and needs further exploration. Also to be explained are the roles of the skin and deep thermal receptors in the regulation of body temperature, especially their relationships to the hypothalamic area of the brain. In an effort to answer these questions, the investigators are conducting studies in animals by studying the electrical activity of the individual nerve cells of the hypothalamic area of the brain. These are being studied in response to various localized and generalized experimental temperature changes, as well as the responses of the skin and deep thermal receptors to controlled temperature changes.

Preliminary findings derived from the initial year of this study reveal:

1. Experiments performed on patches of the camel's fur indicate that at least half of the heat is lost by means of reradiation, reflection, and conduction.
2. Further heat loss is accomplished by the evaporation of water, which accounts for a substantial amount of heat loss.
3. Surplus heat, resulting from maximal thermal exposure, is stored by the animal during the day. By late afternoon, the temperature of the animal may rise to a point very close to 108° F.
4. During the cool of the night, this surplus heat is dissipated so that by morning the animal may reach a temperature of about 90° F.
5. Preliminary experiments have indicated that the temperature of the hypothalamus is lower than rectal or vaginal temperatures of about 2° F.

FUNCTIONS OF PLAY IN DEVELOPING ADULTHOOD

Dr. David Riesman of the University of Chicago, Chicago, Ill., has conducted the project based on the theory that the psychological development of the individual depends in large measure on the quality of his interpersonal relationships. The study was supported by PHS Grant No. M–891. Although much attention and study have been devoted to family relationships such as those between parent and child, there has been very little research on the role of other social relationships in personality development. It was Dr. Riesman's hypothesis that the role of these other, less intimate, social relationships is an important one, since, for example, much of the psychological development of the child and adolescent takes place in social situations. It is in such settings that different patterns of behavior are tried out, practiced, and found successful or unsuccessful. Results of such social experimentation are an important factor in shaping a person's subsequent personality development.

Dr. Riesman hypothesized that, since social activities are chosen voluntarily, such activities would be more likely to reflect an individual's personality than would his participation in nonvoluntary activities. In order to pursue his aims, he chose for study four different social situations. One was a study of close friendships, analyzing the ways they change in time and the influences they have on the personalities of the individuals involved. The second was a study of sociability patterns among professional people and the effects of such patterns on the individual's perception of his professional role. The third study was an analysis of the psychological effects of participation in a social function on the persons attending it. The fourth study, an investigation of social interaction patterns of college students working at a summer camp, focused on the relationships between an individual's social experiences and his level of psychological maturity.

The results of his analyses indicate that the dramatic social and economic changes which have occurred in this country in the past three decades have been accompanied by distinctly different forms of social interaction. Greater economic and social security has resulted, for example, in more time and money to devote to leisure time and social activities.

Dr. Riesman found, however, that the social interactions developed during these leisure time hours are more for the purpose of sharing mutual anxieties than they are on the development of personal resources. For example, one major function of a modern social group is to derive explanations and interpretations of an often complex and bewildering society; the explanations and interpretations secured are usually those which give maximum self-esteem and protection to group members.

Riesman also found that an individual who is going through a period of transition in his life uses a social group situation to obtain reassurances from others about his own importance and self-esteem; this situation is typified by the college student who is breaking away from one family and preparing to establish another. Individuals who spend a majority of time and energy in occupational roles which contribute little to their sense of personal worth also develop social relationships for the purpose of enhancing their feeling of self-esteem and importance.

COMPLEX BEHAVIORAL REPERTOIRES IN CHIMPANZEES

Dr. Charles B. Fuerster of the Institute for Behavorial Research is conducting research on chimpanzees on an NIMH research career development award.

His research belongs to a broad class of experiments in psychology aimed at understanding how an individual acquires and maintains new behavorial patterns. The chimpanzee was chosen as laboratory model because it is the most complex of all primates and most closely approximates man in processes of behavior.

Binary arithmetic was chosen as the framework for these studies of animal behavior because it represents an intermediate intellectual system which can be handled by chimpanzee, by man, and for that matter also by electronic computer, for it is the mathematical language utilized in modern high-speed computers. An animal can identify a number through a series of yes and no responses. Through this system, numbers can be presented as a light, or series of lights, that are on or off. Though unable to "write" decimal numbers, a chimpanzee can "write" a minary number simply by pushing lights on or off.

These experiments have special relevance to many facets of education and training. They provide important clues whereby organisms can be taught new ways of coping with their environment.

Though the concepts that emerge are not literally transferrable in application to man, this research has important applications in solution of many psychiatric problems. It is relevant to the training of the mentally retarded; and concepts being developed indicate ways in which psychotic behavior can be altered through application of techniques derived from such experiments.

A STEREOTACTIC ATLAS OF THE BEAGLE BRAIN

It is now possible for medical scientists to pinpoint specific regions of the brain by external landmarks on the skull. Clinically, this information is extremely important in neurosurgery and in the introduction of radioactivity or electrodes to regions of the brain. Scientifically it provides a new tool in manning the internal structures and regions of the brain.

The development and refinement of these techniques can only be done in animals, and the dog's skull is a particularly useful model.

The Public Health Service is supporting the development of a stereotactic atlas of the dog brain. The project is under the supervision of Dr. Nicholas Wetzel of the Northwestern University, Chicago, Ill. (PHS grant No. B–2196). Such an atlas would enable investigators to use the same baselines in future research. A number of dog brains have been treated so as to provide information on the relation of internal brain structures and external landmarks. The data is being collated and readied for publication. This is a precise and exacting task involving the skills not only of the neuroanatomist but also artists, photomicrographers and the duplication and printing charts. It is expected that the atlas will be published within a year.

BEHAVIORAL AND PHYSIOLOGICAL CONCOMITANTS OF DREAMS

This study is being conducted by Joe Kamiya of aLngley Porter Neuropsychiatric Institute, San Francicso, Calif. (PHS grant M–5069).

Only in recent years has it become evident that dreaming may serve some very important psychological and physiological functions. Dreaming is normally universal and accounts for more than one-fifth of every night's sleep; recent studies of dream deprivation have shown that when dreams are interrupted by forced awakening or by administration of certain drugs, the individual later shows a number of psychological disturbances. For example, he develops feelings of anxiety and tension, and he displays mild memory disturbances and difficulty in concentration; some individuals deprived of dreaming also develop intense hunger. The importance of dreaming is also apparent from the fact that normal persons who are deprived of dreams for several nights, when finally allowed to sleep normally, experience an increased amount of dreaming—as if in an attempt to make up for the earlier lack of dreaming.

Research in dreaming is technically difficult, and until recently few investigators have studied the phenomenon. In the past 2 years, Dr. Kamiya has contributed substantially to the methodology available for studies of dreams, and he has added knowledge about the physiological and psychological processes associated with dreaming. Dr. Kamiya has produced more specific information than has hitherto been available about overall patterns of dreams and the relationship of sequences in the dream pattern to physiological changes—for example, in heart rate and respiration rate. His results have confirmed the important role which dreams and the sleep cycle play in the psychological as well as the physical health of the individual.

THE ORAL HEALTH OF ICELANDIC PEOPLE

By the age of 50 most of our population lose teeth because of periodontal disease. By age 65, almost all the population has suffered from this disease. It is painful, annoying, disabling—and expensive. By studying the incidence of the disease in its different manifestations in different peoples, with different foods, different climate and different customs, we may be in a position to make a sizable contribution to the health and pocketbook of the average American.

A study of the oral health of Icelandic people was undertaken by a University of Alabama team under the supervision of Dr. Joseph F. Volker, dean of the school of dentistry and vice president in charge of health affairs. The study was supported by PHS grant No. D–865. Dr. Volker has both a Ph. D. and a D.D.S. degree, and before heading the Alabama program was the dean of the college of dentistry at Tufts University.

He and his coinvestigators are recognized as outstanding scholars and research scientists and have been deemed well qualified to handle this project.

The facilities to carry out the work are recognized as excellent both in Iceland and in Alabama.

This study takes advantage of the opportunity to correlate many factors—climate, industry, population, drinking water, age, organization—and the relationship of these to the serious problems of tooth decay and oral disease. We can learn from these studies some of the mechanisms involved in cultural change related to oral problems and possibly how to protect our teeth.

The survey has already produced some significant reports presented at the meeting of the International Association for Dental Research, March 1962, and printed in Public Health Reports 77: 594, 1962. The investigators found a higher prevalence of tooth decay and gingivitis in children in Iceland than in those of other nations. The contrast with Alaska was marked. The high rate of gingivitis in children was particularly surprising since periodontal disease in youngsters has not heretofore been considered a significant area of study. If we can determine why the gums of small children in Iceland show disease when the supporting structures of the teeth of those in other countries do not, we may have a most important clue to the dental problem of our own older age groups.

The study of the oral health of the Icelandic people has added to our knowledge of the nutritional factors related to dental diseases at different populations. It is one study among some two dozen to develop comparative information on the effects of diet, urban living, and oral hygiene on dental decay and periodontal disease.

The investigators plan also to study the incidence of facial congenital abnormalities such as cleft lip or left palate. The significance of genetic factors in determining facial clefts is not known, and in the stable Icelandic population some indications might be found.

The investigators have completed and published reports on studies of 600 preschool children and have examined 4,000 persons as a sample for study of the oral health of the entire population with emphasis on identifying subgroups with the highest prevalence of dental disorder.

LONGITUDINAL GROWTH STUDIES ON ANOMALIES OF THE HEAD, D–1064

Since the purpose is a longitudinal study of growth patterns over the entire period of childhood, the investigation will have to be a long-term one, in which repeated measurements must be made of the growth of different parts of the face, throat, nose, pharynx, and larynx. In children who have facial deformities, whether the result of congenital malformation or childhood injury, some structures grow and others do not at each age. Speech patterns vary depending on training and on the anatomic changes.

Dr. Pruzansky and Dr. Lis have recently expanded their survey to include additional numbers of patients at the Illinois State Pediatric Institute (a research and training facility maintained by the State of Illinois, primarily for work in the field of mental retardation). This enables them to have a broader base and also to help more children.

In addition, the group have refined their techniques and developed or acquired new kinds of equipment which permit more complete study particularly of X-rays and speech patterns. For example, they now have a machine with three X-ray heads, giving them simultaneous pictures on a triple axis. They are utilizing metal implant markers (a technique developed by another NIDR grantee), to establish landmarks on the repeated X-ray studies. They are using a new method of reproducing and duplicating X-ray prints. This permits investigators in several institutions to have copies of the X-rays for reference, to exhibit X-rays to groups or to publish them without loss of detail.

Many investigators can use sets of X-rays at the same time or combine them in different ways. This is the equivalent of having reproducible laboratory data. The investigators are also using a nasality meter, a technical advancement in speech machines, to provide standards of measurement in repeated examinations of the nasality of speech.

Since children take many years to achieve full growth of the face and head, it will be perhaps a decade before the total pattern will be clear. The team should by that time find out what structures change and how much, with and without correction; at what ages correction of specific anatomic changes should be made; whether prosthetic or surgical correction at different ages produces better results; whether speech improves by itself or needs specialized therapy; and if therapy is needed, what form it should take and at what ages.

INVESTIGATION OF INFORMATION CONTAINED IN ECHOS

It is recognized that orientation and location of objects is a crucial detriment to useful life among the blind. Numerous attempts have been made to assist the blind in obstacle detection and orientation, but the basic methods by which the blind are able to find their way continue to be through the use of canes, guide dogs, and human guides.

The ability of bats to navigate, avoid obstacles, and apparently detect the form and shape of objects in the absence of light is well developed. A group of investigators from the University of Arizona under the leadership of Dr. Howard Baldwin (PHS grant No. B–2656) has designed a program to duplicate or simulate the physical apparatus used by bats in these processes.

The group's major effort has been spent in developing a miniature sound-generating system which could produce these sonic signals. Although some advancements have been made in reducing the size of certain electronic components, a practical model for use by the blind has not yet been developed.

STUDIES OF SILENT THINKING

Dr. Irving Maltzman of the University of California, Los Angeles, Calif., is conducting research (PHS grant No. M–4684) designed to gain insights into the thought processes of mentally disturbed persons, particularly schizophrenics. Mutism is a prime symptom in the pathology of schizophrenia, and one of the most difficult problems encountered in the study and treatment of the disorder is the patient's unwillingness or inability to say what he thinks or feels.

Dr. Maltzman has perfected a method for studying language and thought processes; the method is particularly adaptable for use with schizophrenics because it includes several physiological measures that can indicate the patient's reactions to words or ideas without his having to respond to them verbally, and it is in this sense that he is studying "silent thinking."

Using this method, Dr. Maltzman has conducted eight major studies in the areas of language and thinking. He has found significant differences between schizophrenic and normal persons in terms of their ability to learn and to respond to verbal material; furthermore, he has found differences between female and male schizophrenic patients. Dr. Maltzman's results to date indicate that the schizophrenic's facility with language, although generally lower than the normal person's, is not uniformly affected by his disorder; his responses are markedly different for highly personal words, for example, as compared with neutral words. Such findings carry important significance in the diagnosis and treatment of mental illness.

RED TUNA AND YELLOW FAT DISEASE IN THE CAT

Scientists everywhere are attempting to find a safe agent which would lower high blood cholesterol levels and would reduce the frequency of abnormal fat metabolism in man. Search for a safe drug of this kind is potentially of great importance to the problem of atherosclerosis. One biomedical research scientist, supported by the National Institute of Arthritis and Metabolic Diseases has reported encouraging results in a study related to the search for such an agent.

This scientist is Dr. Gordon W. Newell, of the Stanford Research Institute, Menlo Park, Calif., whose research project (PHS grant No. A–5194) bears the abstract and misleading title of "Red Tuna and Yellow Fat Disease in the Cat."

Red fish and yellow fat studies seem remote from research to reduce excessive blood cholesterol levels in man, but possible agents for accomplishing this reduction include certain fats found in fish oils. Large amounts of these fats, which are highly unsaturated, are contained in some ocean fish oils. However, before these substances can be used in medical experiments involving the reduction of excessive blood cholesterol levels in man, their safety or possible toxicity must also be investigated. This is important because an unusual disease in cats, yellow fat disease, appears to stem from the toxic action of the fat found in certain species of red tuna. This happens only under special experimental conditions, namely when the meat of these fish is the only food consumed by the cats.

In his present studies, Dr. Newell is attempting to find a way to protect cats fed these marine oils in large quantities, from yellow fat disease. It is possible that the use of antioxidants (substances which hinder oxidation) will overcome the toxic effects, permitting the special fat found in red tuna to be tested for its ability to lower choleserol. Several antioxidants are being tested by Dr. Newell in an attempt to treat or prevent yellow fat disease in experimental animals, before any recommendation is made involving the use of these special red tuna oils by human subjects.

Early results obtained by Dr. Newell have shown that it is possible to inhibit yellow fat disease or keep it under control in many cases through the use of several antioxidants. This is an encouraging finding, and although preliminary, opens the way for further promising results.

Dr. Newell is also using the condition of yellow fat disease in the cat as a test situation which can help to determine what happens, and why, during the process of aging especially when aging is accompanied by longstanding abnormal fat metabolism. Among other manifestations, yellow fat disease causes a deposition within the cat's fatty tissues of an abnormal fatlike substance called ceroid. The longer certain red tuna oils are fed to the cats the greater the accumulation and deposition of this ceroid. Moreover, this unusual fatty substance is highly insoluble, and once it is deposited in the animal's fat tissues, it is extremely difficult for the body's normal chemical processes to remove it.

Dr. Newell has found that ceroid which accumulated when he fed his cats red tuna marine oils in large quantities is still present in their tissues for more than a year after the cats have been switched to a normal diet. He has also found that the special red tuna fats affect the formation or production of hemoglobin, the oxygen-carrying red pigment of blood. In advanced cases of yellow fat disease, the animals—fed exclusively on a diet of red tuna—were found to develop anemia. In this advanced condition, and especially during the terminal stage, the animals also showed typical paralytic symptoms. What Dr. Newell has found in this project is that certain antioxidants are able to inhibit yellow fat disease or keep it under control.

Dr. Newell has also observed that the ceroid material in his experimental animals appears to be very similar to the type of ceroid which accumulates during the aging process in man. He feels that the yellow fat disease in the cat thus could offer an important research tool for the investigation of an important factor involved in human aging.

In order to avoid any popular misunderstanding concernnig the use of tuna meat in the feeding of cats, it is important to emphasize that long-term studies by Dr. Newell have shown that ordinary tuna pet foods for cats, in contrast to the special experimental diets employed by him, are definitely nontoxic and will not cause "yellow fat disease" in cats.

STATEMENTS AND TABLES REQUESTED BY THE COMMITTEE

Mr. Fogarty. We shall place in the record at the conclusion of your testimony the several overall statements and tables we have asked you to prepare, including, of course, the professional judgment budgets of the individual Institute Directors. You will get those to us, will you not?

Dr. Shannon. Yes, sir; we will be glad to.

Mr. Fogarty. That has been the common practice for some time. Now, on the first page of your statement, you said, "I won't pretend today's compromise satisfies me."

NEEDS FOR HEALTH AND MEDICAL RESEARCH NOT BUDGETED FOR

Will you take some time and put into the record some of the limitations in this budget, and all the unmet needs in health and medical research that this budget cannot take care of? You can put that statement in the record.

(The requested comments follow:)

Dr. Shannon's Comments

The request is to identify health research needs not met in the President's budget for fiscal year 1965. To such identification, both an immediate and longer run perspective are pertinent. For additional research opportunities that NIH program operators believe could be met in fiscal year 1965, I refer you to the professional judgment budgets submitted by NIH Institute Directors.

To my mind, however, the longer program view—taking into account planned speed and direction of program growth—is the more important for identification and discussion here.

Let me comment first—and briefly—on the professional judgment budgets:

Certain of the unmet research opportunities identified relate to maldistribution of funds within the inflexibility of a rigid budget structure, resulting in substantial shortages in some appropriations and substantial balances in others. In addition, deficiencies arise from the considerable timegap between the time the budget is developed and the actual budget year. The 1965 budget for NICHD—a new Institute—represents a rather special case: Because of the mechanics of the budget cycle, the estimates for this new Institute had to be firmed up before the new Director had assembled his program staff and had an opportunity to work out reasonably solid program plans. The professional judgment budget for NICHD therefore represents a later and more considered view of its Director. The need stated is for a substantial shift of research grant funds to the collaborative area; and for strengthened efforts in fellowships, training, and direct research.

Similarly a decision to channel sharply increased efforts into promising new research directions raises bugeting problems for the immediate fiscal year; but the more important consideration is agreement on ultimate program levels, and a plan to reach this funding level over several budget cycles. For relevant examples, note professional judgment estimates for NCI's chemical carcinogenesis program, NIAID's vaccine development program, and DRFR's animal and special research resource programs. I believe, too, that for the past several years, rigidities of the budget process have led to understatement of research grants needs of NIAID.

Taking the longer program view, I see these needs that funding levels in the 1965 budget—projected unchanged into the future—would not meet.

I believe prudence requires further strengthening of NIH program administration. With total program running in excess of $1 billion annually, with unusually complex developmental programs to mount and manage, and with ever-present policy and management issues in the extramural area, I see need for strengthening at three points: In grants management, in program planning and analysis, and in the management of scientific and technical information. Strengthening should be in terms both of numbers of positions and of salary levels permitted.

Also in direct operations I see critical need for more adequate future efforts in computer technology—certainly a key area for research growth and effectiveness in the years ahead; and for full development, through construction, of the resource potential represented by animal facilities at the NIH farm in Poolesville.

Extramurally, I note that 1965 funding levels in the fellowship area in most appropriations fall short of program needs anticipated for future years. We will need more fellowships; also program levels will have to go up to pay training costs to institutions participating as well as costs due to standardization of stipend levels. Particularly for the two new Institutes, NICHD and NIGMS, we should expect to see significant growth in both fellowship and training grant areas.

Of key significance to overall NIH programs are deficiencies in some of the research resource programs of DRFR. Throughout the country, further progress in many research directions is related to the provisions of more adequate research facilities and resources. Here the key element is construction and we are now working at the limits of the appropriation authorization in this area. Where certain special research resources are costly—and regional or national in orientation—serious consideration must be given to Federal support for full construction costs.

In like manner, the achievement of program goals for important new developmental research efforts of NIH Institutes will require broader contractual authority than that now possessed by the PHS. The need here is to be able to commit continued support for several year periods and to provide for such construction as is essential to the accomplishment of the contract objectives. I think we will have to move in this direction to get the progress we want, and must have, in key developmental areas such as cancer virus research, pharmacology and toxicology research, chemical carcinogensis, and vaccine development, among others.

Dr. SHANNON. I will just point out, Mr. Fogarty—I will be glad to do that, but when I talked about the compromise, I was really talking about the substance of my remarks, trying to cram into a short period of time all the things I would like to present.

Mr. FOGARTY. Well, this is a compromise, is it not? The budget?

Dr. SHANNON. Yes, sir; it is a compromise between professional aspirations and capabilities and opportunities on the one hand, and realities of availability of funds on the other.

Mr. FOGARTY. So, will you place in the record a detailed statement of all the unmet needs in health and medical research that this budget might be able to make a dent in, or even get started on?

Dr. SHANNON. I will try to do something, sir.

Mr. FOGARTY. I am giving you a lot of leeway.

PERCENTAGE INCREASE BY MAJOR BUDGET ACTIVITY

Mr. FOGARTY. What is the percentage increase by major budget activities?

Dr. SHANNON. In research grants, it is 10 percent; in training and fellowship, 6 percent; direct research, 4 percent; and if you put all others, it is 5 percent.

Mr. FOGARTY. Just about enough to cover increased costs.

EFFECTS OF BALANCE-OF-PAYMENTS PROBLEM ON INTERNATIONAL RESEARCH PROGRAM

I have just one more question: How does the balance-of-payments problem affect your international research program?

Dr. SHANNON. As I understand the situation, about 2 years ago, the Bureau of the Budget became aware of the seriousness of the balance-of-payments problem, and all granting agencies, or all agencies that had serious oversea activities at that point in time were put on notice that they should restrict as much as was reasonable within the mission of their organization those programs that involved the outflow of dollars from the United States.

This was just about the time, actually, when Dr. Martin Cummings was appointed Chief of our Division of International Research. We took this very seriously and actually cut back—on not the actual dollar value, but the rate of increase—because this was a program that was rising roughly parallel with the domestic program. We curtailed the availability of funds, cut out all overhead, and took a rather dim view on those research programs that actually supported the principal investigator.

In addition, fully realizing that this program had no connotation of foreign aid, but was primarily and exclusively and only developed to satisfy domestic needs, we took an increasingly hard look at the substance of research, the support of which was requested, in order to be certain that it did in fact satisfy domestic objectives, rather than an objective which was primarily that of a scientist overseas.

Mr. FOGARTY. You cut back $1.5 million, you say in your statement on page 22.

Dr. SHANNON. Well, it began really a year ago last summer, we committed ourselves to cut back $1 million. This is the second cut, $1.5

million, in Western Europe. We went from $12 million to $9.5 million; and this proposes going from $9.5 million to $8 million.

Now we are proposing a program at the level of $8.5 to $7 million, and in the aggregate from——

Dr. Kidd. $15 to $13.5 million.

Mr. Fogarty. How is this $1.5 million cut this year going to affect the balance of payments?

Dr. Shannon. I am not an economist, Mr. Fogarty, but from where I sit——

Mr. Fogarty. If I were an economist, I think I could prove by increasing this budget that you could help the balance of payments.

Dr. Shannon. It will not solve the problem, I am sure.

Mr. Fogarty. Do you have an economist on your staff?

Dr. Shannon. Yes, sir; Dr. Kidd.

Mr. Chairman, there are a couple of things that relate to foreign support of science overseas that I would like to call to your attention. Because of their deep interest and concern to me, I think they would also be of interest to the committee.

Apart from all other considerations, what is not commonly appreciated is that the health sciences are being pursued overseas primarily for domestic purposes. Nonetheless, they have had and do have a profound effect not only on the United States but on the entire international field. I would like to touch on three items that highlight this.

Mr. Fogarty. Excuse me, Doctor, I have a long-distance call. Would you put those in the record?

(The requested information follows:)

Domestic Need for Support of Research Abroad

Few of the health problems of the American people are unique. Most of them are equally serious problems for other countries. Therefore, a natural basis exists for establishing collaboration in attacking common problems. The National Institutes of Health has in recent years increased its support of foreign scientific resources in order to accelerate the acquisition of new biomedical information and thus improve the health of the American people. The successful pursuit of this goal requires that, wherever possible, we make use of the original ideas, unusual interests, and competence of foreign investigators; of special geographical, cultural, and social conditions and of exceptional laboratory facilities. Thus, the efforts of our own highly trained scientists in certain fields are being reinforced by grants affording partial support for outstanding foreign scientists working on projects of mutual interest.

An example of Public Health Service support of research abroad involving an unusual environment is the grant (NB–03637–02) made to Dr. Ernst Herbert Barany, department of pharmacology, University of Uppsala, Uppsala, Sweden. Research on glaucoma, one of the major causes of blindness in the world, is handicapped by the lack of a suitable experimental animal host. Dr. Barany, a leading ophthalmologist and physiologist, has found several species of monkeys with a clinical entity virtually identical to human glaucoma. By employing glaucomatous monkeys it is now possible to investigate the pathogenesis, natural history, and therapy of glaucoma. This should result ultimately in a better understanding and treatment of human glaucoma. The work of this Swedish scientist is currently closely associated with the studies of Dr. M. F. Armaly (University of Iowa, grant No. NB–03636–02), who has been a highly regarded investigator of glaucoma. The collaboration of these two scientists is undoubtedly resulting in a more productive effort than if their work were to proceed independently of one another.

Another type of cooperative international investigation (supported by the National Institute of Neurological Diseases and Blindness) is the cooperative study of blood groups and chromosomes under the direction of Dr. Diamond of the Harvard Medical School in conjunction with several European specialized laboratories of outstanding caliber. This exemplifies the utilization of multiple, broadly based resources and skills to derive scientific insights not possible through the relatively isolated effort of individuals or single groups confined to a single country. Among the recent dramatic breakthroughs in neurological disease research has been the identification of mental retardation and other neurological diseases developing in infancy and childhood with chromosomal aberrations and with abnormal blood groups. Kernicterus, a crippling form of mental retardation, and cerebral palsy are often associated with the Rh factor. Recently, Turpin and Lejeune (Kennedy Award winner) demonstrated the presence of an extra chromosome (No. 21) as forming the genetic basis of mongolism. These discoveries have opened an entirely new vista of research. As a result, Dr. Diamond, a blood grouping expert, has inaugurated a cooperative study of blood groups and chromosomes in conjunction with a group of European laboratories where much of the original work was done and which are noted for their specialized skills and facilities. Included in the project are the University Institute for Medical Genetics at Uppsala, Sweden, under the direction of Nobel laureate, Professor Book, a discoverer of chromosomal abnormalities as the cause of not only mental retardation, but also of conditions previously thought to result from brain damage (porencephaly); the Department of Medical Genetics at the University of Turin, in Italy, under the direction of Professor Cepellini, who is internationally known for his research on blood groups, immunology, and genetics; the Institut de Progense of the Faculty of Medicine, in Paris, under the direction of Professor Turpin and Dr. J. Lejeune; the Department of Clinical Pathology, of the Royal Marsden Hospital, in London, under the direction of Dr. H. E. M. Kay, who is actively investigating areas of immunohematology and cytogenetics; and the Central Laboratory of the Blood Transfusion Service of the Netherlands Red Cross, under the direction of Dr. J. J. van Loghem, who is one of the outstanding blood grouping authorities in Europe.

The grant in support of the work of Dr. Harry Heller, Tel-Hashomer Government Hospital, Tel Aviv, Israel (A–2857) was awarded primarily to make use of resources, including clinical material, not readily available in the United States, and secondarily because Dr. Heller is an outstanding worker with 40 years of experience in metabolic research. Familial Mediterranean fever (FMF) affects mainly, if not exclusively, people of mediterranean origin. Many Americans fit this genetic picture and the disorder is no uncommon in the United States. Nowhere in this country, however, does a population concentration suitable for FMF research exist comparable to that which exists in and near Tel Aviv. Dr. Heller and his associates have made considerable progress on the development of a reliable diagnostic test for FMF. Presently, only characteristic clinical cases can be diagnosed with any degree of certainty, while many atypical cases go undiagnosed. Moreover, other disorders are sometimes misdiagnosed as FMF. The new test is based on the detection of an abnormal protein fraction in the serum of patients with the disease, a protein which Dr. Heller's group originally discovered. Not only is this test expected to be of great value to the United States, but the cost of this investigation if it could be conducted in this country, would be at least three to four times its cost in Israel.

Mr. DENTON. This international program is where foreign countries do research for the NIH, is that right? Not for foreign countries.

Dr. SHANNON. This is basically the situation; but I will put it in another way: They do research that is of interest to them, but out of what they wish to do, we only select those things that satisfy our program needs.

In other words, this is a highly specific program.

Mr. DENTON. The U.S. Government has to pay foreign scientists for this research work?

Dr. SHANNON. Only partly, sir; this is a sharing of the costs.

AVAILABILITY OF COUNTERPART FUNDS

Mr. DENTON. Why do you not pay them with counterpart funds? That would not affect the balance of payments one way or the other.

Dr. SHANNON. We do, sir, in those areas in which those funds are available.

Mr. DENTON. They are funds that can only be used in that country.

Dr. SHANNON. This is correct.

Mr. DENTON. Are not those funds available in most countries?

Mr. KELLY. In Western European areas, there are no foreign currencies available owned by the United States.

Dr. SHANNON. There are small balances that are used to produce emphasis and things of that sort, but available for general purposes, no, sir.

Mr. DENTON. They are paying their debt in money that can only be left in those countries?

Mr. KELLY. No, sir.

Mr. DENTON. Are you sure about that?

Mr. KELLY. Yes sir; the countries today that have excess foreign currencies are not countries in Western Europe, sir. As Dr. Shannon says——

Mr. DENTON. Where do they get these counterpart funds?

Mr. KELLY. There were payments made under the original Marshall plan and under the AID program, which are now still being repaid, but they are not excess to what we normally spend in that country, and therefore are not available for the conduct of such programs as this foreign research. In other places, like Israel, India, Pakistan, and so forth, we are using exclusively foreign currencies for the conduct of programs in such countries.

RESPONSE TO CRITICISM OF GOVERNMENT OPERATIONS COMMITTEE

Mr. DENTON. A year ago, the Government Operations Committee was rather critical about some operations of the NIH. You spent quite a bit of time explaining your side of it.

Is there anything more that you would want to say this year, along that line, or would you rather put something like that in the record?

Dr. SHANNON. I would be glad to put a statement in the record, but I would like to say a word or two at this point in time.

I think we have accommodated our programs to the major criticisms that have been brought out by Mr. Fountain, and I think the program is stronger because of the criticism.

I might say this has caused us a substantial effort, but I think it has been productive of better managed programs.

Mr. DENTON. Would you want to put a statement in the record about that?

Dr. SHANNON. I will be glad to.

(Information to be furnished follows:)

ACTIONS TAKEN BY PUBLIC HEALTH SERVICE TO STRENGTHEN THE ADMINISTRATION OF ITS RESEARCH AND TRAINING GRANT PROGRAMS

In a report issued in April 1961, the Committee on Government Operations made several recommendations for improving the administration of NIH's research and training grant programs. On previous occasions, the Public Health Service has reported to that committee and to the Committee on Appropriations on a number of actions taken to strengthen research and training grants administration; the most recent report to the Appropriations Committee was in March 1963.

Since that report, the PHS has continued to take steps aimed at further strengthening of its mechanisms for administering research and training grants programs. There follows a summary of some of the specific steps taken within the past year:

1. *Redistribution of grants management functions.*—In May 1963, the Surgeon General issued to the Public Health Service bureau chiefs a formal document defining: (a) those research grants management functions to be performed on a decentralized basis by PHS institutes and program divisions; and (b) those to be performed on a centralized, PHS-wide basis by the Division of Research Grants. The resulting distribution of functions is designed to: (a) strengthen central resources for coordinating the development of administrative and fiscal policies and procedures that apply to PHS research grant and award programs; and (b) enable PHS institutes and program divisions to review individual research grants and grant programs more intensively. A formal report of progress was submitted to the Surgeon General on June 28, by each of the Service's bureaus, and there continue to be significant additions to, and strengthening of, the grants management staff in both the Division of Research Grants and in the PHS institutes and program divisions.

2. *Revision of certain administrative procedures involving grantee institutions.*—The PHS has established a number of conditions requiring PHS approvals that formerly could be made by grantee institutions. In administering these provisions, it has become increasingly evident that the grantee institutions, rather than the PHS, may be the more appropriate site for making these individual decisions. The NIH recently completed the first phase of a study of the possible transfer to grantee institutions of authority for making certain of these decisions. It was concluded that this transfer authority would be made in a degree commensurate with the development of the grantee institution's administrative capability to exercise the authority in an objective, responsible fashion. It will be essential, however, that grantee institutions make these decisions through formal review mechanisms within the grantee institutions and within documented procedures that have been described by the grantee institution and approved by the PHS. The second phase of this study will begin shortly to test the feasibility of this approach among a sampling of grantee institutions.

3. *Planning for geographically dispersed grants administration.*—The Director, NIH, has previously advised the Appropriations Committe of NIH's plans to establish a pilot installation in Boston to test the feasibility of geographically dispersed grants administration. During this past summer a PHS study team devoted full time to studying this question. All PHS research granting organizations were consulted, and a large sampling of grantee institutions in the Boston area were contacted to obtain their advice. A formal study report recommending how a pilot office might be organized and staffed in Boston was completed, and the plan to open the office was approved by the Surgeon General.

We are holding this plan in abeyance, however, in view of the current policy limiting Federal employment and in the light of higher NIH management priorities.

4. *Improving the communication of research and training grant policies.*—Several steps have been taken to improve the communication of research and training grant policies. The Research Grants Manual, originally issued in January 1963, has been thoroughly revised to include a number of substantive policy changes and to improve its clarity. The revised manual has been distributed to grantee institutions, and its provisions will go into effect April 1, 1964. A new manual covering the management of all the training grants of the PHS is in final draft and will be issued by the beginning of fiscal year 1965. The first set of regulations governing the administration of grant programs for the support of health-related research projects has been published in the Federal Register. Early in January 1964, the PHS began a series of seminars for business managers of grantee institutions to review and interpret grants management policies and procedures in the research grants manual. Additional seminars will be held periodically so that ultimately a large number of grantee institutions can be accomodated.

5. *New payment procedure.*—NIH has recently made a basic change in the procedure for payment of research grants that will make cash available on a basis consistent with actual needs for the entire PHS research programs in an

institution. Under this plan, a grantee institution submits a monthly cash request for the succeeding month. This request for cash advance is based on the estimated cash expenditures, and includes a provision for a contingency allowance on the estimated cash requirements for the subsequent month. This new plan is designed to limit the payment amount to the immediate needs of a grantee institution, thereby avoiding the accumulation of surplus Federal funds in grantee institutions.

6. *Revised application form for research grants.*—The research grants application form has been revised to obtain more comprehensive information about the investigator's resources and the administrative and fiscal aspects of his proposal. This should enable scientific review groups to make more refined judgments concerning the competence of the applicant, the adequacy of his resources, the merits of his proposal, and the reasonableness of his research approach.

7. *Establishment of a Committee on Training Grants Data.*—A Committee on Training Grants Data, comprising NIH staff members, was established in November to recommend improvements in current methods for collecting data on the number of trainees under grants and their characteristics. A system will be developed to produce routinely more timely and detailed information. This will permit each NIH institute and division to collect and analyze whatever data, in addition to the core data for all of NIH, it considers necessary for the discharge of its program responsibilities. The committee has set July 1964 as a target date for the completion of its study.

Mr. DENTON. That is all.

Mr. Lesinski?

CRITERIA FOR TERMINATING INTERNATIONAL RESEARCH PROJECTS

Mr. LESINSKI. Dr. Shannon, regarding Mr. Fogarty's and Mr. Denton's remarks about the international research program, as I have gone through your reports, I find them very informative and, for the most part, full of excellent ideas and results. But irrespective of whether the results might be argumentative—and I am in full accord, of course, with what you are doing there—but when is this program going to be phased out?

Dr. SHANNON. Most of the things I think we are doing overseas now we would not plan to phase out, because they are being done for our purposes, doing certain things we cannot do in this country, and taking advantage of certain unique opportunities.

Let me mention some very specific ones. I will not try to go over this program by program, but I will give some of them.

The Cancer Institute, over the past 4 or 5 years, has developed to the point where we are finally getting clarification of one of the characteristics of population groups that modify the distribution of cancer within the body. Two studies are underway that have been very revealing; study of cancer in Japanese, as they reside in Japan, as they reside in Honolulu, as they reside on the west coast, and this will be extended to as they reside in Latin America.

Mr. LESINSKI. That is right.

Dr. SHANNON. It costs substantial sums to have this information collected for our purposes. But here you have homogeneous population groups that generally do not intermarry when they leave their homeland, but are, nonetheless, exposed to quite different environments—food, habits of living, and so forth.

Interestingly enough, this hits the heart of the genetic susceptibility to cancer; as the Japanese moves between environments, the characteristics of his susceptibility change from that of a Japanese in Japan to that typical of a Japanese in Honolulu or on the west coast.

Mr. LESINSKI. Typical of the rest of the people at the same time, or among the various ethnic groups?

Dr. SHANNON. Yes. Now, we are doing much the same thing with groups of Norwegians. We are supporting a study of the Cancer Registry in Norway and will pick up comparable Norse population groups in the North-Central States, again for comparative purposes of this sort.

Let me take another quite different area and again show why it is to our advantage to do this. About 6 or 7 years ago, the upsurge in clarifying work in the field of genetics, on a cellular level, was just beginning in this country. It so happened that one scientist in France, using viruses and bacteria as the experimental tools of the work—this was a man by the name of Mineaux, at the Pasteur Institute of Paris—had techniques which were far in advance of our techniques in this area. He was the outstanding person in the world at this particular specialty. It was to our advantage to broaden his thought and, in addition, to place some of our people in training situations with Mineaux.

The interesting thing here is that Professor Mineaux visited NIH to give one of our NIH lectures last Thursday, I believe it was, and he was remarking at dinner at the striking change that had taken place in our broad competence in cellular biology in this 5-year period. This was taking advantage of knowledge abroad.

We can point out a number of similar situations.

Another area is in the Cancer Institute in London, where the advances in chemical understanding of problems of carcinogenesis were far in front of our own work. We supported that quite broadly. Again, this is our own self-interest that is involved here.

So that as we select these programs, we attempt to support only that which provides a unique opportunity for us, which will not be found within our American programs.

Now, these programs do not provide stable support or long-term support; these grants are limited to a segment of time—3 years is the maximum. When they are reviewed, it is from this standpoint: Has the need been satisfied, and can the work now be supported in the United States?

Mr. LESINSKI. I am in full accord with the intention, Doctor. For instance, your study of plants in various parts of the world, as far as wanting to determine the diet of individuals in relation to cancer of the stomach, greater disturbances of the stomach with the Irish than with the Italian, and so forth, I am in full accord; but how long do you have to keep on saying the Irish and Italian? Get down to basic facts and compile the facts and make a determination. That is what I am trying to find out.

To study is fine, but to not come up with any practical answer——

Dr. SHANNON. I think we are coming up with very factual answers. I think if you look at our program from year to year, you will see the changes. We do not simply select a topic and keep studying the same thing for an indefinite period.

Mr. LESINSKI. It seems that way to me. That is the reason I brought it up.

Dr. SHANNON. Well, it may seem that way to you, sir, but you must realize, if it does seem that way, it is because to tie down any of these facts will occupy a period of 3 to 6 years. It can rarely be demonstrated in a short time.

Mr. Lesinski. In other words, may I, in all fairness to my question, to myself, when you say that, after you study the problem, but an attempt to find out an answer—it might take you 4 or 5 or 6 years to find it out, then you phase it out?

Dr. Shannon. We are in the process now of doing just that.

I point out, the program is really so young, that we are just now reaching the place where we can see that program objectives have been accomplished in various areas, so that we are in a position to begin shutting down.

We have had discussions over the past 3 months, in Sweden, in the United Kingdom, in France, in the Netherlands, and in Belgium, which anticipate an orderly retreat from our present support position in those countries, but in such a fashion that programs can be picked up for a long-term support by the local country if it desires.

The conversations have taken place—I participated in some in London 3 or 4 weeks ago, and Mr. Kidd has just spent 2 weeks in discussing these very things at these countries.

I do not believe, on the other hand, that as we move out of one opportunity, others may not emerge. And the international aspect of science is such that we feel that it is imperative that we be allowed to move out and get such specific competence addressed to our problems. In other words, though we do not need the individual grantee on a continuing basis, the mechanism must remain available on a continuing basis.

Mr. Lesinski. You had a study in Mexico where cancer of the uterus is prevalent. This is fine to find these things out, I mean, but take the Mexican and the Japanese, the point being simply this: I am all in accord with your intention to find out—wonderful, we should know more about it—but now, if we keep on dragging this thing out, it costs the taxpayers money.

Dr. Shannon. No; this study for the Japanese will be terminated when these facts are tied down and completely understood.

The study will move then, on the other hand, into the environment and will attempt to determine what in the environment is different in Japan than in the United States or Hawaii or in Chile.

Mr. Lesinski. Which is good.

Dr. Shannon. These are the four countries which are selected for study. So that the character of the study changes—different portions will be done by quite different scientists in these areas, with quite different competence, even as in our country the work will move to another group. But it still becomes important for us to have access to such talents outside the United States.

This is a wholly selfish point of view.

Mr. Lesinski. I am in full accord with that; no argument. The only thing I said before, when the study is completed, stop.

Dr. Shannon. With this we would agree.

CANCER GRANTS IN 1965 BUDGET

Mr. Lesinski. How many cancer grants do you have this year, in the 1965 budget?

Dr. Shannon. Dr. Endicott is here and can give you the precise figures.

Dr. Endicott. For the record, I will supply it. It is on the order of 1,000—1,700.

Dr. Shannon. 1,700.

Mr. Lesinski. You start out with 1,000 back in the 1963 budget, and we now try to hold you back in the 1964 budget. Now in the 1965 budget you have 1,700 of them.

Mr. Kelly. In 1964 we have 1,678 research grants in cancer, and 1,460 of these were continuations of grants which had been made in 1963 or earlier, and 218 of them were new grants. In 1965, it is anticipated that we will have 1,711 grants, 1,492 of which will be continuations of grants which were made in 1964 or earlier years, and 219 new ones.

DIFFERENCE BETWEEN ENGINEERING AND SCIENCE

Mr. Lesinski. Mr. Kelly, may I use a parallel here?

Say I am a bricklayer or supposed to be a bricklayer. As a doctor is supposed to know something about cancer, I am to be taught how to lay brick, plumb a wall, lay a straight course of brick, and so forth?

Dr. Shannon. Yes, sir.

Mr. Lesinski. Why should I be taught, or why should I spend my time finding out how to make brick and mix mortar, wasting my time in these various things, when it should be proven first as to how the brick can be made, how much heat should be used in a kiln, how much lime to mix with the mortar, how much sand to mix with the mortar, and so forth? I am to be taught how to lay brick—period.

What you are doing here evidently with the cancer grants, is, you are trying to bring up students in not how to teach them how to lay brick—or organisms of cancer—but you are trying to bring them into other fields or phases of cancer, and they may end up not knowing a thing about cancer.

Your intent is right, but I again repeat, you are scattering yourself too thin and not getting down to the brass tacks as far as cancer is concerned.

Excuse me, your intent and purpose is to teach students about cancer, and have them taught the aspects of cancer also while learning in school to become a doctor. But I still say you are deluding yourself.

Dr. Shannon. Well, Mr. Lesinski, I could not agree less, sir.

I would like to take your analogy of a bricklayer in building a building, and I think I would like to say, first, that in order to appreciate my point of view, and the one I would like to pose, is that I would point out that there is a difference between engineering and science.

Now, in engineering, one knows precisely what one wants as the end result. One knows the elements of design that will be required to produce the end structure that one wishes to build, or the instrument one wishes to design, and one has access to knowledge concerning the characteristics of the material that is needed to put the instrument or house together.

Mr. Lesinski. Dr. Shannon, at this point you claim, or the NIH claims that there is no cure for cancer, as such, per se; right?

Dr. Shannon. Yes, sir.

Mr. Lesinski. With the exception of cutting it out or sterilizing the area.

Mr. Denton. There are one or two cases——

Dr. SHANNON. One or two cases.

Mr. LESINSKI. One or two cases. Therefore you have no actual cure of cancer, as such, per se?

Dr. SHANNON. Yes.

Mr. LESINSKI. You are still delving in an unclear area. You are spending many, many dollars trying to teach individuals about cancer, for which there is no cure today, at this time.

Mr. KELLY. May I make a comment? Perhaps I gave wrong information or inappropriately responded to your question. I thought you wanted to know how many research projects we were supporting.

Mr. LESINSKI. That is right.

ORGANIZATION FOR RESEARCH ON CANCER

Mr. KELLY. These research projects are not teaching mechanisms. This is the support of scientists who are endeavoring to find what causes cancer, how it could be treated, how it could be cured, or how it could be prevented. These are not teaching projects, or teaching grants, but these are the support of scientists who are endeavoring to fill in the unknown knowledge.

Mr. LESINSKI. In colleges?

Mr. KELLY. Universities and colleges represent probably the largest single area of research undertaking.

Mr. LESINSKI. That is right.

Mr. KELLY. Although it does include hospitals and nonprofit research organizations.

Mr. LESINSKI. But the point is, you have too much duplication, my friend.

Dr. SHANNON. Mr. Lesinksi, this is not correct.

Mr. LESINSKI. You are bound to have duplication, with 1,700 of them.

Dr. SHANNON. You said "too much duplication."

Mr. LESINSKI. That is correct.

Dr. SHANNON. I say we have duplication—this is purposeful duplication.

At the stage of knowledge of the cancer process that we are at at the present time, we face very many broad unknowns. For us—with this broad deficiency of our knowledge as to what constitutes the fundamental defect in the cell that permits it to take off and form a cancerous growth—were we to decide we could settle it by one or two approaches that were selected by a committee at Bethesda, and then to organize science to adjust itself to that, this would put us in a ridiculous position. We do not yet have the facts to develop a reasonable working hypothesis that carries us to the end of the picture.

As a result, we go about it in quite another way. We say that cancer is a result of some abnormal happening within a cell, and the interaction of this abnormal cell when exposed to bodily contaminants or varying hormones.

We approach it from the standpoint of how to find out more about genetic characteristics of the cell. This determines the characteristic of the cell. We try to find out more about the biochemistry of how the cell behaves under a variety of stresses. This determines the reactivity of the cell. We try to determine how this cell reacts to exogenous agents, whether they are carcinogenesis in the way your cigarette or my cigarette——

Mr. Lesinski. It is foolish to smoke.

Dr. Shannon. All of these things. What is the clue to this type of cellular interaction that results in the abnormal growth? What are the relationships between these cells and the body as a whole?

We know you can transfer normal tissue. We know also that in experimental animals, if you transfer a cancer cell, it will grow and reproduce itself. Under certain circumstances, if it dies, you know the body has developed an immunity, and you could no longer transplant that type of cell.

So you have a whole host of immune processes here. You know that certain cancer cells depend on hormone variations. They will grow rapidly or be suppressed, depending on the hormone mixture.

So cancer research, as such, must take off from the basic understanding that something abnormal has happened to a cell, and that from that point on, it passes through a series of systems, leading in some cases to the development of a full-grown cancer. What we attempt to do in cancer research is to remedy the deficits of knowledge at each step insofar as we can determine.

Now, since the end result is not known except that one has a mass that can kill, this in large measure is exploratory research, and you cannot draw a map for Columbus to discover North America. If you are going to find it, you have to send a number of people out, and they will free range within the area of their competence. It is this type of information that will progressively permit the evolution of reasonable hypotheses.

There are a few points along the line where you do have fairly substantial knowledge. These are in certain aspects of cancer chemotherapy and virology. Here you have highly organized efforts to satisfy the need for determinable information.

This whole spectrum of research in all of these areas must go on if the facts upon which to base a workable cancer hypothesis are to be obtained.

If you take the 1,700 projects that Dr. Endicott's Institute is working on, they are a mixture stretching from end to end of the research spectrum.

This is the best we can do.

Mr. Denton. Would it not be a good idea for Mr. Lesinski to go out to your Institutes and go over those different grants with you? Let him see what they are?

Dr. Shannon. We would very much like to have him.

Mr. Lesinski. Dr. Shannon, I have to concur that the approach that you have outlined here, you have to try to trace back every facet. I am in full concurrence with your position. But I cannot wholeheartedly subscribe to having this done in a buckshot manner.

Getting back to what Mr. Kelly said a while ago—either you informed me or Dr. Shannon informed me last year that you purposely had these grants at universities so you could have them in conjunction with student studies, where you have the experience going on, and they could be learning at the same time, which is fine in certain areas. But in cancer, you do not have the knowledge, you do not have the answer. Therefore, the student learning in a university of that type, with a cancer grant going on, is going to make it very valueless. But of course it is research, it is true.

I honestly and sincerely believe that in spite of the fact you said here you have to approach it from all different areas, I have to agree with that point, but you seem to have scattered yourself so far into the wind, I doubt if you will get the points together.

Dr. SHANNON. Well, sir, all I can say is, it is our judgment we are not spreading ourselves too thin.

I recognize that the developmental programs of NCI are costly, both in time and scientific effort. But here is where you get the black or white answer. If you are right, you are right; but if you are wrong, your work is largely for naught.

So we are very careful not to prejudge the facts and set in motion a broad developmental program without a sound working hypothesis.

KREBIOZEN

Mr. LESINSKI. In Illinois, why did two drug firms try to buy a drug from a doctor for a price, and he refused? Just because an individual—now you have proven it wrong, that is fine, if you are right—but why is it that when a drug firm comes out with a new idea, it is fine, but when someone else comes out with a proven idea, it is wrong?

Dr. SHANNON. What is this specific——

Mr. KELLY. Krebiozen.

Dr. SHANNON. Oh. I can tell you about this from two standpoints, Mr. Lesinski. In the first place, the drug industry as an industry is regulated. Individuals in this country, fortunately, are not regulated.

Mr. LESINSKI. Why can the drug industry put something on the market which you may or may not know is proper, and, when an individual comes up with an answer, you automatically turn him down?

Dr. SHANNON. In the first place, under our present law, it is impossible for a drug company to do precisely what you postulate.

Mr. LESINSKI. I beg your pardon, there are many on the market that, after a year or so, you have proved are bad. You know that for a fact.

Mr. KELLY. May I comment, Mr. Lesinski? There was a change in regulations a little over a year ago. The Harris-Kefauver bill was enacted, which modified the responsibilities of the Food and Drug Administration in the handling of new drug applications and, at the same time, the Secretary changed the regulations to prevent the use of experimental drugs that were not approved prior to their use experimentally by the Food and Drug Administration.

It is true that up until a year and a half ago that new drugs could not be sold in interstate commerce without having been approved by the Food and Drug Administration for use, but experimental drugs could be used by patients, by doctors for patients without this prior approval. This is no longer true. Every experimental drug must be approved by the Food and Drug Administration before it is used in interstate commerce, and this change makes it such that there is nobody that can put a drug either on the market or use it experimentally in interstate commerce without prior Federal approval.

Mr. LESINSKI. I suppose you are using the emotions of people in the United States, the emotion involving needs for a cure in cancer, which is essentially only to make yourself do a larger and larger amount of research and expend more Federal funds without getting down to brass tacks.

The thing is cancer is a great threat today, and some cancer cure should be found. But, at the same time, you are putting yourself in a position of letting the American public, in their emotional desire to get a cure, take the bull by the horns and scatter yourself around the whole world. I think it is bad and wrong.

No more questions, Mr. Chairman.

Dr. SHANNON. I will have to respond to that.

Mr. LESINSKI. Yes; you may.

Dr. SHANNON. Mr. Lesinski, I just cannot agree that this is the situation we find ourselves in. Without arguing, I can just disagree.

Mr. LESINSKI. Well, go ahead, Dr. Shannon.

Mr. DENTON. Is there anything more you would like to say?

Dr. SHANNON. I just say, I just disagree.

Mr. DENTON. I would suggest this one thing, we have all heard a lot of Krebiozen. I think when we get to cancer, we ought to ask about that.

Another thing, I would like to suggest the cancer group go over their different grants with you, Mr. Lesinski, so you can see what they are doing. And they can show you some highlights of what they are doing.

I think that is the best way to get at it.

Mr. LESINSKI. I appreciate the chairman's suggestion.

Mr. DENTON. Of course, they do not pass on the drugs; Pure Food and Drug does that.

Mr. LESINSKI. I am aware of that. The point I am driving at is that an individual pharmaceutical company does put drugs on the market with just casual review by the Food and Drug Administration, without delving into the actual facts, and results of the drug, until years later when they find out there are adverse responses from the general public.

Now, if a private individual should come up with an idea, the Food and Drug Administration automatically turns it down without even getting into it.

Mr. KELLY. If that is on the record, I would like to respond.

Mr. LESINSKI. Go ahead.

Mr. KELLY. I think there is no difference in the review which is made by the Food and Drug Administration, irrespective of who files the application, and that that review is not casual.

Mr. LESINSKI. But the only difference is the Food and Drug Administration and the HEW bent over backward to assist the proponents or the manufacturer of the drug industry.

Mr. KELLY. We hope what we are assisting is the American people.

Mr. LESINSKI. I would be very happy to be wrong in what I had said here.

Mr. DENTON. We shall adjourn until 2 o'clock.

(The following are the statements referred to earlier by the chairman:)

HISTORY OF THE 1965 NIH BUDGET

SUMMARY

Chronological development of overall budget for 1965

[In thousands of dollars]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	767,813	−157,865	609,948	−29,086	580,862	−28,709	552,153
Fellowships	68,249	−19,090	49,159	−1,573	47,586	−1,937	45,649
Training	229,585	−35,245	194,340	−14,293	180,047	0	180,047
State control programs	10,950	−4,200	6,750	0	6,750	0	6,750
Total grants	1,076,597	−216,400	860,197	−44,952	815,245	−30,646	784,599
Direct operations:							
Research	86,150	−8,252	77,898	+300	78,198	−2,050	76,148
Collaborative studies	93,494	−28,832	64,662	0	64,662	−286	64,376
International research	1,614	−462	1,152	−83	1,069	+78	1,147
Computer research and technology	4,390	−3,024	1,366	−1,366	0	0	0
Biologics standards	5,634	−559	5,075	0	5,075	−83	4,992
Training activities	2,521	−621	1,900	−215	1,685	−85	1,600
Professional and technical assistance	6,802	−2,302	4,500	−300	4,200	+24	4,224
Review and approval	20,209	−3,403	16,806	−1,150	15,656	−93	15,563
Program direction	6,523	−894	5,629	−799	4,830	−112	4,718
Total direct operations	227,337	−48,349	178,988	−3,613	175,375	−2,607	172,768
Total obligations	1,303,934	−264,749	1,039,185	−48,565	990,620	−33,253	957,367

EXPLANATION OF CHANGES—OVERALL NATIONAL INSTITUTES OF HEALTH

DHEW action

The major change in the preliminary estimate to the DHEW and the subsequent estimate to the BOB was in research grants. The NIH proposed support for the payment of all continuations, supplementals, and new grants. The Department approved payment of all committed research grant projects, but maintained support of competing, supplemental, and new grants at approximately the estimated 1964 level. Other significant reductions by the Department in the research grants activity were general research support grants from $50 to $45 million; general clinical research centers from $29.9 to $27.9 million; hospital improvement grants from $18 to $12 million; and special resource centers from $9 to $8.2 million.

Reductions were made in training grants and fellowships in the amount of $15.9 million. This represents an increase of $55.6 million over 1963 obligations, and $13 million over estimated 1964 programs.

The changes in the direct operations programs were of a general nature related to estimates of staffing needs, research contract requirements, and reductions in amounts proposed for grants. During this phase of the review, reduced estimates for the computer research and technology function were combined with the direct research activity.

Bureau of the Budget action

Reductions of $30.6 million made by the BOB were primarily in the grants programs and affected noncompeting continuations, supplementals, general research support grants, and mental health hospital improvement grants. An amount of $1.9 million for the research career awards was also eliminated from the proposed fellowships program.

Changes in the direct operations areas were based on further reductions in proposed staffing requirements.

Estimates as approved by the BOB include provision for staffing related to new mental retardation legislation, the commissioned officers' pay increase, and a proposed stipend increase in the fellowships program.

GENERAL RESEARCH AND SERVICES

Development of 1965 budget estimates for general research and services

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$166,464	−$52,007	$114,457	−$5,659	$108,798	−$3,627	$105,171
Fellowships	22,149	−5,925	16,224	−509	15,715	−750	14,965
Training	56,731	−19,049	37,682	−500	37,182	0	37,182
Total grants	245,344	−76,981	168,363	−6,668	161,695	−4,377	157,318
Direct operations:							
Collaborative studies	2,000	−685	1,315	0	1,315	0	1,315
International research	1,614	−462	1,152	−83	1,069	+78	1,147
Computer research and technology	4,390	−3,024	1,366	−1,366	0	0	0
Training activities	315	−150	165	+85	250	−85	165
Review and approval	5,362	−1,929	3,433	−670	2,763	+66	2,829
Program direction	1,291	+64	1,355	−334	1,021	−50	971
Total direct operations	14,972	−6,186	8,786	−2,368	6,418	+9	6,427
Total obligations	260,316	−83,167	177,149	−9,036	168,113	−4,368	163,745

BIOLOGICS STANDARDS

Development of 1965 budget estimates for biologics standards

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Direct operations:							
Biologics standards	$5,634	$−559	$5,075	0	$5,075	−$83	$4,992
Total direct operations	5,634	−559	5,075	0	5,075	−83	4,992
Total obligations	5,634	−559	5,075	0	5,075	−83	4,992

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Development of 1965 budget estimates for child health and human development

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$36,300	+$474	$36,774	−$1,710	$35,064	−$346	$34,718
Fellowships	4,000	−1,300	2,700	−278	2,422	−58	2,364
Training	11,000	−3,700	7,300	−3,020	4,280	0	4,280
Total grants	51,300	−4,526	46,774	−5,008	41,766	−404	41,362
Direct operations:							
Research	1,623	−954	669	+352	1,021	−730	291
Collaborative studies	1,980	−1,580	400	0	400	+37	437
Training activities	362	−262	100	−100	0	0	0
Review and approval	1,296	−783	513	+223	736	−254	482
Program direction	561	+130	691	−127	564	+33	597
Total direct operations	5,822	−3,449	2,373	+348	2,721	−914	1,807
Total obligations	57,122	−7,975	49,147	−4,660	44,487	−1,318	43,169

NATIONAL CANCER INSTITUTE

Development of 1965 budget estimates for National Cancer Institute

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$79,275	−$11,335	$67,940	−$1,873	$66,067	−$3,683	$62,384
Fellowships	4,100	−15	4,085	−104	3,981	−39	3,942
Training	9,000	0	9,000	0	9,000	0	9,000
Total grants	92,375	−11,350	81,025	−1,977	79,048	−3,722	75,326
Direct operations:							
Research	18,042	+546	18,588	+336	18,924	−328	18,596
Collaborative studies	60,469	−16,269	44,200	0	44,200	−16	44,184
Review and approval	1,913	+165	2,078	−99	1,979	0	1,979
Program direction	1,074	−67	1,007	−100	907	−30	877
Total direct operations	81,498	−15,625	65,873	+137	66,010	−374	65,636
Total obligations	173,873	−26,975	146,898	−1,840	145,058	−4,096	140,962

NATIONAL INSTITUTE OF MENTAL HEALTH

Development of 1965 budget estimates for mental health activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$112,458	−$15,056	$97,402	−$8,806	$88,596	−$12,101	$76,495
Fellowships	11,377	−2,600	8,777	−347	8,430	−373	8,057
Training	83,000	0	83,000	−9,787	73,213	0	73,213
State control programs	10,950	−4,200	6,750	0	6,750	0	6,750
Total grants	217,785	−21,856	195,929	−18,940	176,989	−12,474	164,515
Direct operations:							
Research	13,779	−2,240	11,539	−198	11,341	−138	11,203
Collaborative studies	4,949	−963	3,986	0	3,986	0	3,986
Training activities	1,463	−175	1,288	−200	1,088	0	1,088
Professional and technical assistance	6,802	−2,302	4,500	−300	4,200	+24	4,224
Review and approval	3,990	−681	3,309	−83	3,226	+38	3,264
Program direction	1,077	−337	740	−66	674	−37	637
Total direct operations	32,060	−6,698	25,362	−847	24,515	−113	24,402
Total obligations	249,845	−28,554	221,291	−19,787	201,504	−12,587	188,917

NATIONAL HEART INSTITUTE

Development of 1965 budget estimates for National Heart Institute

[In thousand]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$121,222	−$26,989	$94,233	−$3,528	$90,705	−$2,924	$87,781
Fellowships	8,000	−1,700	6,300	−31	6,269	−62	6,207
Training	16,984	−2,000	14,984	0	14,984	0	14,984
Total grants	146,206	−30,689	115,517	−3,559	111,958	−2,986	108,972
Direct operations:							
Research	11,732	−212	11,520	+371	11,891	−346	11,545
Collaborative studies	2,471	−435	2,036	0	2,036	−85	1,951
Training activities	282	0	282	0	282	0	282
Review and approval	2,329	−53	2,276	−90	2,186	+21	2,207
Program direction	493	−6	487	−55	432	+9	441
Total direct operations	17,307	−706	16,601	+226	16,827	−401	16,426
Total obligations	163,513	−31,395	132,118	−3,333	128,785	−3,387	125,398

NATIONAL INSTITUTE OF DENTAL RESEARCH

Development of 1965 budget estimates for National Institute of Dental Research

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$13,131	−$3,324	$9,807	−$347	$9,460	−$45	$9,415
Fellowships	2,263	−1,052	1,211	0	1,211	−12	1,199
Training	5,050	−76	4,974	−266	4,708	0	4,708
Total grants	20,444	−4,452	15,992	−613	15,379	−57	15,322
Direct operations:							
Research	4,701	−1,120	3,581	−15	3,566	−84	3,482
Collaborative studies	1,065	−500	565	0	565	0	565
Review and approval	681	−98	583	−18	565	−11	554
Program direction	453	−231	222	−7	215	−3	212
Total direct operations	6,900	−1,949	4,951	−40	4,911	−98	4,813
Total obligations	27,344	−6,401	20,943	−653	20,290	−155	20,135

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Development of 1965 budget estimates for arthritis and metabolic disease activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$93,895	−$7,156	$86,739	−$3,141	$83,598	−$3,337	$80,261
Fellowships	7,500	−2,800	4,700	−215	4,485	−506	3,979
Training	21,300	−6,800	14,500	−810	13,690	0	13,690
Total grants	122,695	−16,756	105,939	−4,166	101,773	−3,843	97,930
Direct operations:							
Research	13,735	−1,515	12,220	−223	11,997	−130	11,867
Collaborative studies	1,891	−294	1,597	0	1,597	0	1,597
Review and approval	1,723	−225	1,498	−54	1,444	+47	1,491
Program direction	534	−193	341	−33	308	−17	291
Total direct operations	17,883	−2,227	15,656	−310	15,346	−100	15,246
Total obligations	140,578	−18,983	121,595	−4,476	117,119	−3,943	113,176

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Development of 1965 budget estimates for allergy and infectious disease activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$66,818	−$26,255	$40,563	−$1,423	$39,140	−$167	$38,973
Fellowships	5,560	−2,498	3,062	0	3,062	−86	2,976
Training	9,720	−1,720	8,000	+239	8,239	0	8,239
Total grants	82,098	−30,473	51,625	−1,184	50,441	−253	50,188
Direct operations:							
Research	14,264	−2,203	12,061	−209	11,852	−237	11,615
Collaborative studies	12,414	−7,129	5,285	0	5,285	0	5,285
Review and approval	1,345	+37	1,382	−302	1,080	−33	1,047
Program direction	525	−154	371	−44	327	−17	310
Total direct operations	28,548	−9,449	19,099	−555	18,544	−287	18,257
Total obligations	110,646	−39,922	70,724	−1,739	68,985	−540	68,445

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Development of 1965 budget estimates for neurology and blindness activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1965 President's budget
Grants:							
Research	$78,250	−$16,217	$62,033	−$2,599	$59,434	−$2,479	$56,955
Fellowships	3,300	−1,200	2,100	−89	2,011	−51	1,960
Training	16,800	−1,900	14,900	−149	14,751	0	14,751
Total grants	98,350	−19,317	79,033	−2,837	76,196	−2,530	73,666
Direct operations:							
Research	8,274	−554	7,720	−114	7,606	−57	7,549
Collaborative studies	6,255	−977	5,278	0	5,278	−222	5,056
Training activities	99	−34	65	0	65	0	65
Review and approval	1,570	+164	1,734	−57	1,677	+33	1,710
Program direction	515	−100	415	−33	382	0	382
Total direct operations	16,713	−1,501	15,212	−204	15,008	−246	14,762
Total obligations	115,063	−20,818	94,245	−3,041	91,204	−2,776	88,428

PROFESSIONAL JUDGMENT BUDGETS

SUMMARY

The Directors of the several Institutes and chiefs of the program divisions of the National Institutes of Health have submitted estimates for 1965 which reflect in their best professional judgment the total funds which could be used for their individual programs.

These estimates have not been influenced by the Office of the Director, National Institutes of Health, the Office of the Surgeon General, or the Office of the Secretary through guidelines or review such as normally occur in the budgetary process. They do not, therefore, represent in the aggregate an NIH budgetary proposal. Consideration has not been given to those factors which normally influence budget proposals, such as—

(1) The consistency of the proposals of individual Institutes with existing congressional directives and legislation.

(2) The appropriateness of relative emphasis among programs as for example between research grants and training grants.

(3) The adequacy of manpower, space, and other resources when the total budgets of all Institutes are added up.

(4) The effect of combined Institutes' proposals upon educational institutions.

(5) The sum total of all proposals in relation to fiscal feasibility and other broad policy considerations.

(6) The effect of projected program increases upon the central (NIH) management requirements.

GENERAL RESEARCH AND SERVICES

Comparison of 1964 appropriation, 1965 President's budget, and 1965 professional judgment budget estimate

[In thousands]

	1964 appropriation	1965 President's budget	1965 professional judgment budget estimate	Difference
Grants and related contracts:				
Research (ICMRT)	$3,000	$3,000	$3,500	$500
Fellowships (international postdoctoral)	1,200	1,200	2,400	1,200
Total, grants and related contracts	4,200	4,200	5.900	1,700
Direct operations:				
International research	1,061	1,147	1,197	50
Training (IRCDP)	156	165	215	50
Total, direct operations	1,217	1,312	1,412	100
Total estimate	5,417	5,512	7,312	1,800

The professional judgment of funds that could be effectively applied to this appropriation exceeds the President's budget by $1,800,000. This excess could be used as follows:

1. Research and related contracts

A. *Research grants (ICMRT)*.—The International Centers program, now entering its fourth year of operation, has promoted the establishment of five U.S.

university-sponsored ICMRT's. These are characterized by domestic and oversea facilities devoted to collaborative effort in biomedical research and research training of particular interest to the American scientific community. Utilizing the international capabilities of scientists representing many disciplines, integrated and comprehensive programs for the study of all health problems, as well as those relating to medicine in the tropics, have emerged from the Centers located in Colombia, Costa Rica, India, Malaysia, and Pakistan.

Preliminary reports emanating from the International Centers indicate that they are making significant research contributions in a variety of biomedical disciplines, that they are introducing a substantial number of younger scientists into the field of international research each year and that they have become important foci of research and research training activity in the host nation. Research grant support for each university-sponsored unit has been maintained at approximately $500,000 annually. This has provided base support for the Centers during their developmental phase. Expansion of scientific staff and the necessity for additional research facilities required to undertake long-term multidisciplinary studies contribute to the need for additional base support. An amount of $500,000 could provide for modest expansion of each of the five International Centers for Medical Research and Training.

The creation of a sixth International Center located in Africa, south of the Sahara, is being seriously considered during fiscal year 1965. Excellent opportunities, established facilities and other resources readily available in selected areas have made this setting most attractive to several U.S. universities which are submitting their proposals for consideration by the Advisory Committee on International Centers. An estimated $500,000 could finance a new Center in Africa through its first year of operation.

B. *Fellowships* (*International Postdoctoral*).—International postdoctoral fellowships are awarded to promising foreign scientists for training in biomedical research in the United States. Forty-one countries participated in the international postdoctoral fellowship program in fiscal year 1964. Each country, through a nominating committee, submitted its recommendations for fellowships. These nominations were competitively reviewed by the International Fellowship Review Panel at NIH.

It is estimated that in fiscal 1965, 220 applications for support will be received. Because the screening mechanisms of the country nominating committees is most selective, a high rate of approvals by the Fellowship Review Panel may be expected. The average cost of an international postdoctoral fellowship is $9,000 per year. Acceptance of these new approvals and selected continuations will cost $2,400,000.

2. Direct operations

A. *International Research.*—An amount of $50,000 and five positions could provide supporting staff for existing, as well as additional program requirements. The assignment of personnel under the career development program requires selection of oversea sites for training having due consideration for the past training and future plans of these personnel, and periodic evaluation discussions at the site with trainee and his laboratory supervisor. Two positions could therefore be employed in the administration of the international career development program.

The international postdoctoral fellowship program requires a staff equipped to furnish professional guidance to the foreign fellow, as well as matters of personal and private nature, cultural relations, customs and laws and regulations of the United States. Three of the new positions could be assigned in these areas for the present, as well as the future, increased workload.

B. *Training* (*IRCDP*) *Activities.*—This program was originally planned for the continuous training of a minimum of 20 career development personnel. Timing delays required that the program be reduced to 10 positions for these career development personnel. Experience has shown that this program will contribute to the medical research manpower of this country. Since the program of 10 positions was completely committed for 1965 by early 1964, three new positions could provide for continuity and long-range flexibility.

DIVISION OF RESEARCH FACILITIES AND RESOURCES, GRS

1965 professional judgment budget

[Dollars in thousands]

	1964 estimate		1965 President's budget		1965 professional judgment budget	
	Positions	Amount	Positions	Amount	Positions	Amount
Grants:						
Research:						
General clinical research centers		$27,145		$27,684		$28,900
Special research resources		5,685		8,200		15,300
Scientific and technical information resources						3,000
Primate centers		5,700		7,000		9,000
Animal resources						8,500
General research support grants		[1] (35,000)		[1] (40,000)		[1] (60,000)
Health research facilities construction		[2] (50,000)		[2] (50,000)		[2] (185,000)
Centers for research on mental retardation		(6,000)		(8,000)		(16,000)
Total grants		38,530		42,884		64,700
Direct operations:						
Collaborative studies		315		315		2,000
Review and approval	104	1,083	108	1,230	133	1,600
Program direction	31	378	31	409	35	480
Total, direct operations	135	1,776	139	1,954	168	4,080
Total, DRFR	135	40,306	139	44,838	168	68,780

[1] The general research support grants program is administered by this Division and supported by a percentage levied against each of the 9 Institutes Public Law 86–798 and is not included in the total.

[2] The budget for health research facilities construction includes centers for research on mental retardation and is a separate budget. The amounts for these two programs are not included in this total.

The professional judgment of funds that could be effectively applied to all activities exceed the President's budget by $23,942,000. This excess could be applied as follows:

1. Research grants

A. General clinical research centers, difference of $1,216,000:

1964 program	$27,145,000
1965 continuations and supplements	25,400,000
1965 new projects	3,500,000
Total 1965	28,900,000

This amount could support approximately seven new centers. Program objectives are being achieved through awards to institutions such as medical schools and research hospitals for the establishment of special discrete clinical research centers together with specialized supporting or core laboratory facilities and stable, well-trained staffs. The centers permit intensive studies in clinical research and extend laboratory experience into valid studies in the human. The units are provided for multicategorical and multidepartmental research, in which preclinical and clinical scientists with a variety of research interests and techniques share the special facilities. Additional centers could be established in new areas of clinical medicine such as organ transplantation and human development.

B. Special research resources, difference of $7,100,000:

1964 program	$5,685,000
1965 continuations and supplements	8,300,000
1965 new projects	7,000,000
Total 1965	15,300,000

This amount could provide specialized or unusual facilities and resources required for research in the medical and related sciences, computer and scientific data processing, biomedical engineering, bioinstrumentation, and biomathematics; steroid methodology and analysis resources to support the study of assay procedures and their application to the study of biochemical human profiles in health and various diseased states; cell and tissue culture resources for the cultivation and preservation of normal and diseased mammalian cells and tissues, and the support of investigations concerning the development of procedures for making these valuable materials more easily available to qualified investigators; specialized biochemical resources in which appropriate methodology for the isolation, analysis and characterization of proteins, lipids and other important cellular materials could be investigated and developed for the benefit of biomedical investigators; tissue and organ transplantation resources designed to support the multidisciplinary and multicategorical investigations of many investigators in their studies of these complex phenomena and interrelationships.

C. Scientific and technical information resources, difference of $3,000,000:

1964 program	(1)
1965 new projects	$3,000,000
Total 1965	3,000,000

[1] No funds.

The amount of $3 million could support various types of scientific and technical information resources. These include technical information centers, medical documentation and communication projects, specialized centers for rapid handling of data and information and experimental health sciences information resources.

D. Primate and animal resources centers, difference of $10,500,000:

1964 program	$5,700,000
1965 continuations and supplements	10,500,000
1965 new projects	7,000,000
Total 1965	17,500,000

This amount could provide for continuations and supplements for the seven regional primate research centers and $7 million for the establishment of two regional centers of laboratory animal medicine, a center for the breeding of some rarer types of primates necessary for projects in medical research, research animal resources for special genetic strains for cancer research and highly specialized investigations which are in short supply, and a special program for raising and conditioning baboons for organ transplant work and other biomedical research.

E. General research support grants (difference of $20,000,000) (supported by each of the 9 Institutes and administered by this Division):

1964 program	$35,000,000
1965 program	60,000,000
Total 1965	60,000,000

This amount could support approximately 298 institutions already receiving general research support and approximately 55 additional institutions expected to qualify in 1965. The general research support grant could be extended to cover university components other than health professional schools in 1965 at approximately $10 million and $5 million for establishment of three model health research center awards for research and research training.

F. Health research facilities construction (difference of $135,000,000):

1964 program	$50,000,000
1965 program	185,000,000
Total, 1965	185,000,000

This amount could provide funds for payment of approved but unpaid applications of $49 million from 1964, and of $50 million for the 1965 program, additional research facilities projects resulting from the impact of the medical teaching facilities program of $40 million, provision of facilities for animal resources, $25 million, and funds for special facilities such as hyperbaric laboratories and tissue and organ transplantation centers, $21 million.

G. Construction of centers for research on mental retardation (difference of $8,000,000):

1964 program	$6, 000, 000
1965 program	16, 000, 000
Total, 1965	16, 000, 000

The $16 million could support construction of four to five centers for research on mental retardation and related aspects of human development.

2. DIRECT OPERATIONS

A. Collaborative studies, difference of $1,685,000.—This is a contract mechanism used for close review and control of certain projects. The $2 million could provide some contracts for certain special research resources, highly specialized animal resources, permit studies to set standards for facilities construction, and fund projects in scientific and technical information.

B. Review and approval, difference of $370,000.—This amount could provide funds for 29 additional positions for the expanded research grants program and health research facilities construction program.

C. Program direction, difference of $71,000.—This amount could provide funds for four positions for the overall planning, evaluation, direction, and coordination of the programs of the Division of Research Facilities and Resources.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

1965 professional judgment budget

[In thousands]

	1964 estimate	1965 President's budget	1965 professional judgment budget
Grants:			
Research	$55, 431	$59, 287	$68, 261
Fellowships	13, 307	13, 765	17, 135
Training	35, 682	37, 182	47, 157
Total grants	104, 420	110, 234	132, 553
Direct operations:			
Collaborative studies	1, 000	1, 000	1, 500
Review and approval of grants	1, 519	1, 599	2, 314
Program direction	548	562	616
Total direct operations	3, 067	3, 161	4, 430
Total estimate	107, 487	113, 395	136, 983

The professional judgment of funds that could be effectively applied to this appropriation exceeds the President's budget by $23,588,000. This excess could be used as follows:

1. GRANTS

A. Research grants

	1965 President's budget	1965 professional judgment budget	Difference
Regular program:			
Continuations:			
Noncompeting	$31,122,000	$34,043,000	$2,921,000
Competing	3,610,000	6,210,000	2,600,000
Supplemental	1,262,000	1,908,000	646,000
New grants	14,227,000	16,460,000	2,233,000
Additional indirect costs:			
(*a*) At 20 percent	2,269,000	2,549,000	280,000
(*b*) At 25 percent	756,000	850,000	94,000
Total regular program	53,246,000	62,020,000	8,774,000

An additional amount of $6,167,000 over the President's budget could effectively be used for continuation and supplemental grants. An amount of $2,921,000 could be used for noncompeting continuation grants in 1965, based on an analysis of actual commitments for grants active and/or awarded during 1964. An amount of $3,246,000 would be used to support additional high priority competing continuation and supplemental awards, based on experience factors as applied to the total regular 1964 program.

An amount of $2,233,000 over that provided in the President's budget for new grants would permit the expansion of research in selected disciplinary areas. These areas include the further development of multidisciplinary biomedical engineering programs, a few of which have already been started, and the expansion of the Institute's activities in the support of research in the basic health-related behavioral sciences. The rapid development of new theories in the broad area of molecular biology and the increased refinement of techniques and instrumentation, as well as the availability of increased numbers of trained personnel, will allow appropriate expansion in this very promising field. Plans are now being completed for the 1965 expansion of research in pharmacology, toxicology, and medicinal chemistry, an area of nationally recognized importance.

Additional concomitant indirect costs are estimated at $374,000 over the amounts provided in the President's budget.

Scientific evaluation and planning grants

An additional amount of $200,000 would be used to establish more study sections to review the increasing number of grant applications and to support the costs of additional site visits by study section members.

B. Fellowships

	1965 President's budget	1965 professional judgment budget	Difference
Predoctoral	$5,273,000	$7,193,000	$1,920,000
Postdoctoral	1,774,000	2,474,000	700,000
Special	577,000	927,000	350,000
Research career	6,141,000	6,541,000	400,000
Total	13,765,000	17,135,000	3,370,000

In recent years several studies have emphasized the urgent need for increasing our national effort to train manpower for medical research. The NIGMS fellowship program is essential in terms of complementing the larger research training grant program by providing opportunities for advanced training in research specifically tailored to the needs of the individual.

The major portion of the adidtional funds, $2,970,000, would be used to finance an increased number of regular followships in such shortage areas as biomathematics, biomedical engineering, biophysics, experimental pathology and surgery, pharmacology and toxicology. The remaining $400,000 would be used for the research career program. Program details are as follows:

Predoctoral.—The amount of $1,920,000 over the President's budget includes $192,000 for increased stipends and $1,728,000 for the support of 320 additional awards in 1965, thereby bringing the total number of predoctoral fellows to 1,200.

Postdoctoral.—An additional amount of $700,000 would support 100 additional new awards, resulting in a total program of 360 awards in 1965.

Special.—An additional amount of $350,000 would enable the support of 35 additional candidates, particularly in the fields of pharmacology and toxicology; thus bringing the total number to 100 in 1965.

Research career program.—An additional amount of $400,000 would finance 20 new awards, thereby establishing a program level of approximately 400 awards by the end of fiscal year 1965.

C. Training

	1965 President's budget	1965 professional judgment budget	Difference
Continuations:			
Noncompeting	$28,607,000	$28,607,000	-------------
Competing	6,220,000	9,000,000	$2,780,000
Supplementals	480,000	3,100,000	2,620,000
New grants	1,675,000	6,200,000	4,525,000
Scientific evaluation grants	200,000	250,000	50,000
Total	37,182,000	47,157,000	9,975,000

An amount of $47,157,000 would permit the normal growth of outstanding and productive training programs. Additionally, this amount would allow the funding of important new programs established to produce an enlarged corps of competent researchers to help meet the predicted acute shortage in the general medical sciences a few years hence. The critical research manpower needs developing in the biomedical sciences represent an imbalance created over a long period, and will take a relatively long period to overcome. For instance, the majority of the graduate training programs funded by NIGMS grants have been in operation only for a period of 3 years and have yet to graduate their first class. The growth of many programs initiated 3 or more years ago was recently reviewed by expert non-Government consultants. This experience showed that after careful negotiations renewals necessitate an average increase in funding of nearly 50 percent per program. These increases provide for the addition of more trainees to established programs, thereby increasing the efficiency of the basic investment.

An additional amount of $2,780,000 could be advantageously utilized in 1965 for additional competing continuations. Of the total amount of $9 million, $8 million would be used to support about 120 of the most worthy applications, and $1 million would bring the fiscal year 1964 grants up to the support level indicated by progress made in training program development.

An additional amount of $2,620,000 could be used in 1965 to support additional supplemental grants which are expected to be approved by the Council.

An amount of $6,200,000 could be advantageously used for new training grants programs. Highlighted for increased support would be the medical scientist program, the clinical research training program and the complex of clinical pharmacology and toxicology, where the manpower requirements have been spelled out with great emphasis in the press and by congressional committees. The difference of $4,525,000 would also enable the initiation of additional new programs in such important graduate areas as biophysics, biomathematics, behavioral sciences, biochemistry, biomedical engineering, and the challenging multidisciplinary areas of biology and medicine.

An additional amount of $50,000 could be used to support increased costs of scientific evaluation grants—primarily to add a new training committee to share the increased review load.

2. DIRECT OPERATIONS

A. Collaborative studies, difference of $500,000

An additional amount of $250,000 could be used to expand the hospital computer project, which is being supported by contract. This expansion of the project, which is aimed at organizing a computer system adapted to the biomedical research needs within a hospital, would consist of (1) extending user programs to cover as many functions within the hospital as are capable of being adapted, and (2) demonstrating regional applicability by adding another hospital to the study.

The remaining amount of $250,000 would be used to support continuations of other contracts which were initiated and/or converted from grants in prior years.

B. Review and approval, difference of $715,000

An additional amount of $268,000 could advantageously be used in this activity to support 39 additional positions to (1) strengthen the staffing of functions responsible for administering the extramural programs of the Institute and (2) provide for necessary and proper staffing commensurate with the expansion of the grants programs.

An amount of $300,000 could advantageously be used to accomplish, by contract, an evaluation of the Institute's training grant programs.

An additional amount of $147,000 is provided for payment to the NIH management fund.

C. Program direction, difference of $54,000

An additional amount of $50,000 would be used to support four positions in the Program Analysis Branch of the Institute. This Branch is responsible for accumulation and analyses of data, and the preparation of scientific and technical reports on the Institute grants programs; additional staff and funds for this function would enable augmentation of data currently being produced and expansion into additional programs. This amount would also support one additional position to strengthen the administrative functions in the Office of the Director.

An additional amount of $4,000 is included for payment to the NIH management fund.

BIOLOGICS STANDARDS

1965 professional judgment budget

[In thousands]

	1964 estimate	1965 President's budget	1965 professional judgment budget
Direct operations	$4,817	$4,992	$5,185

The professional judgment of funds that could be effectively applied to this activity exceeds the President's budget by $193,000. This excess could be applied as follows:

One position and $6,000 for additional supportive assistance on the legal staff; $30,000 and 4 positions in the surveillance of clinical studies which is a new formal function of the Division; $35,000 and 7 positions to augment the staff responsible for the preparation, testing, maintenance, and distribution of physical reference preparations for licensed biological products; 10 positions and $84,000 to increase the number of inspectors and investigators required to perform blood bank inspections and investigate complaints, irregularities, and possible violations of the Public Health Service Act; and 4 positions and $38,000 for establishment of a Pharmacology Section which would evaluate pharmacological studies conducted by manufacturers on biological products.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	1965 professional judgment budget
Grants:			
Research	$25,656	$34,718	$32,718
Fellowships	2,364	2,364	3,564
Training	4,142	4,280	6,880
Total, grants	32,162	41,362	43,162
Direct operations:			
Research	111	255	1,815
Collaborative studies	427	437	2,437
Training activities			100
Review and approval	355	401	468
Program direction	400	568	568
Total, direct operations	1,293	1,661	5,388
Total, NICHD	33,455	43,023	48,550
Reimbursement to management fund	108	146	322
Total estimate	33,563	43,169	[1] 48,872
Construction:			
Temporary mammalian developmental biology facility	(----)	(----)	(150)
Permanent mammalian developmental biology facility (planning)	(----)	(----)	(225)
Total	(----)	(----)	(375)

[1] The amounts included under the professional judgment column exceeds the 1965 President's budget by $5,703,000. The programs identified in this document do not represent a request for additional funds; they merely indicate how the National Institute of Child Health and Human Development could use these funds.

RESEARCH AND RELATED ACTIVITIES, INCREASE OF $1,800,000

A. Research grants, decrease of $2 million

It is our professional opinion that the total mission of the Institute could be accomplished most effectively by moving $2 million from research grants into collaborative studies. This will provide a better balanced program since we believe we can better accomplish some of our research objectives through contractual arrangements rather than research grants.

B. Fellowships, increase of $1,200,000

	1965 President's budget		1965 professional judgment	
	Positions	Amount	Positions	Amount
Postdoctoral	84	$630,000	119	$891,000
Special	45	334,000	64	473,000
Research	88	1,400,000	138	2,200,000
Total	217	2,364,000	321	3,564,000

Postdoctoral and special fellowships, increase of $400,000.—The NICHD training committee recognizes the fellowship program as providing a unique opportunity in the development of personnel for careers as investigators. It is a highly flexible program providing individuals at different stages of development with support for research training in selected areas. As a mechanism it is well suited to support more senior individuals and is most effective in directing and developing scientists in the terminal phase of their training. This program is of considerable significance to the Institute as a means of encouraging individuals to develop a cross-disciplinary approach. Such an approach is most desirable for an Institute which is dedicated to the study of the organism through certain phases of its development, rather than concentrating on categorical disease area.

An increase of $400,000 would allow for additional candidates in reproductive biology, adult development and senescence, mental retardation, congenital malformations, pharmacology, and human communications. It is in these areas that training must be vigorously stimulated in the next few years. We have appointed special consultants to review these areas and determine how we can effectively provide more effective and extensive training. Our Institute should be prepared to take these findings and provide the resources necessary for training deserving young scientists.

Research career development awards, increase of $800,000.—The number of well-qualified candidates nominated for these awards next year is expected to increase as a result of greater needs in programs such as the six mentioned above. An increase of $800,000 would permit NICHD to keep pace with the increased need in the area.

C. Training, increase of $2,600,000

	1965 President's budget	1965 professional judgment
Reproductive biology	$996,000	$1,609,000
Perinatal biology	715,000	1,156,000
Growth and development	1,476,000	2,233,000
Adult development and senescence	155,000	412,000
Mental retardation	460,000	745,000
Congenital malformations	119,000	195,000
Developmental pharmacology	119,000	195,000
Human communications	150,000	245,000
Subtotal	4,190,000	6,790,000
Scientific evaluation and planning grants	90,000	90,000
Total	4,280,000	6,880,000

Of primary importance to our long-range objective of developing successful research programs is the development of excellence in our training programs. This excellence demands an environment composed of inspiring investigator teachers, stimulating research, and adequate facilities and ancillary personnel. An institution's own resources, supplemented by research funds, can provide for a portion of these needs. But it has become clear in reviewing the patterns which have emerged at the NIH that the awarding of a training grant most often determines whether or not a strong and well-balanced approach to the long-range objectives eventually evolves. The NICHD has emphasized the need to develop personnel for academic career. Individuals so equipped will in turn train others and the Institute has identified this approach as the one which will most effectively utilize its resources available for training.

The National Advisory Council in conjunction with our training committee has endorsed the need for establishing programs of research training in medical schools where the present programs in reproductive biology, embryology, developmental pharmacology, congenital malformations, and aging are carried on either on small scale or are completely nonexistent. The training committee also recognizes that the establishment of effective research training programs in veterinary colleges holds considerable promise, particularly in the field of mammalian reproduction. Heretofore, these areas have not had special consideration. Development of excellent training programs in these areas is the best means of producing the trained manpower not currently being provided.

Equally important is the expansion of established training activities in the other program areas of the Institute. This expansion is to meet the demand for qualified manpower for academic positions and positions in research institutes. Expansion of training programs does not usually represent spiraling cost per trainee but rather increased numbers of trainees being supported. Concurrent with this expansion is the trend to increase the period of preferred training. This has contributed significantly to the need to expand the number of trainees if the demands for manpower are to be met.

Recognizing the need to support training in areas heretofore not developed as well as to allow for expanding programs, it is most desirable that our efforts in training be enlarged and intensified in fiscal year 1965.

DIRECT OPERATIONS

Direct research

[In thousands]

	1965 President's budget		1965 professional judgment	
	Positions	Amount	Positions	Amount
Reproductive biology	12	$135	17	$285
Perinatal biology	10	120	15	270
Growth and development			6	74
Adult development and senescence			52	700
Mental retardation			6	74
Developmental pharmacology			8	180
Congenital malformations			6	166
Human communications			6	66
Subtotal, research	22	255	116	1,815
Reimbursement to NIH management fund		36		201
Total, research	22	291	116	2,016

INTRODUCTION

During 1964, the National Institute of Child Health and Human Development has been tooling up to meet the challenge in President Kennedy's message recommending establishment of this Institute.

"We look to such an Institute for a full-scale attack on the unsolved afflictions of childhood. It would explore prenatal influences, mental retardation, the effect of nutrition on growth, and other basic facts needed to equip a child for a healthy, happy life. It would, in addition, stimulate imaginative research into the health problems of the whole person throughout his entire lifespan—from infancy to the health problems of aging." Up to now, the Institute has been very successful in attracting some of the top scientific talent available in the areas under our charge. These people can, and will, through their combined skills as scientist-administrators and laboratory investigators, make significant contributions toward the closing of vast gaps of knowledge presently existent in all of our initial program areas.

Aging research units, 52 positions, $700,000 increase:

Personnel compensation	$228,900
Other objects	149,100
Contracts	322,000

An amount of $227,000 would provide support for 52 positions for a direct research program and $473,000 for the support of these positions and the initiation of contractual programs which would complement and expand the excellent work presently carried on by the Gerontology Branch of the Heart Institute. A direct research program in the National Institute of Child Health and Human Development would provide Federal participation with universities and other institutions now engaged in outstanding research in gerontology. Each of these research units will consist of a team of scientists assigned to laboratories focusing on different aspects of the aging process and assisting in the training of young scientists in this field.

Primate Research Unit, 40 positions, $845,000 increase:

Personnel compensation	$174,000
Other objects	116,000
Contracts	544,000

These funds could provide the means for establishing comprehensive research programs at primate centers by both the assignment of our own scientific teams to these centers, or a contractual arrangement with the universities whereby they would provide the scientific and supportive staff. These units would eventually be returned to the Bethesda area as space became available.

Studies would be done principally in the areas of: (1) reproductive biology, including fertility, conception, and implantation, embryogenesis and fetal development; (2) studies of perinatal biology; (3) developmental pharmacology; and (4) congenital malformations.

Mammalian Developmental Biology Unit, 2 positions, $15,000 increase:

Personnel compensation	$9,000
Other objects	6,000

In keeping with our objectives, we could use two positions and $15,000 for planning a mammalian development biology unit. The basic purpose would be the pursuit of fundamental knowledge about biology of mammalian development. It would provide a resource of several mammalian species (sheep, dogs, swine, etc.) and laboratories required for separate research approaches. Construction items required for the support of this program are discussed in attachment A.

Collaborative studies

[In thousands]

	1965 President's budget		1965 professional judgment	
	Positions	Amount	Positions	Amount
Clinical research:				
Reproductive biology	------	------	6	$120
Perinatal biology	------	------	6	120
Growth and development	8	$74	6	120
Adult development and senescence	2	17	2	40
Mental retardation	8	74	8	160
Developmental pharmacology	3	30	4	80
Congenital malformations	------	------	4	80
Human communications	5	50	4	80
Subtotal, programs	26	245	40	800
Communications:				
Scientific information	8	49	28	324
Public information	7	43	9	78
Conferences	3	100	5	300
Subtotal, communications	18	192	42	702
Field studies: Epidemiology and biometry	------	------	20	935
Total, collaborative studies	44	437	102	2,437

Clinical research units, 14 positions, $555,000 increase:

Personnel compensation	$61,300
Other objects	40,800
Contracts	452,900

This amount could be used for the establishment of approximately three clinical research units with existing medical centers for studies of pregnancy, childbirth, prematurity, and problems of the newborn. We expect to initiate clinical investigations in normal behavioral development in children and adolescence with special emphasis on learning and related problems. These units would be staffed jointly by NICHD and participating governmental and nongovernmental agencies and institutions.

Clinical teams which include professionals such as: Pediatric-neurologists, psychiatrists, psychologists, social workers, public health nurses, educators, dentists, audiologists, speech therapists, and nutritionists, would be assigned to these clinical units. They would be responsible for evaluation of patients and would supply needed information for those conducting basic, as well as clinical research. A few proposed studies are listed as examples:

1. Clinical evaluations of anticonvulsant medications in retarded, epileptic children;
2. Clinical psychopharmacologic research in mentally disturbed subnormal children;

3. The use of growth promoting agents in retardates who manifest growth failure;
4. Psychosocial studies of mental retardation;
5. Dietary treatment of children with specific inborn errors of metabolism;
6. Determine racial differences in prevalence of specific anomalies and the effects of racial admixture on prevalence.
7. Study of selected parameters in populations and families with high frequencies of malformations.
8. Search for susceptible animal systems for study of teratogenic viruses.
9. Search for new teratogens.
10. Explain teratogenicity of thalidomide.

Communications, 24 positions, $510,000 increase:

Personnel compensation	$105,000
Other objects	70,000
Conferences and contracts	335,000

This amount could be used for the employment of an operations analyst to plan and monitor the total information system for NICHD. This system would include technical and public information, conferences, liaison, and cooperation with the other Institutes, Divisions, and facilities of NIH, with the NLM, and with other agencies and organizations of the Federal Government. It could plan for maximum visibility to grantees and intramural scientists of research and development plans and current work as well as of past work in subject fields of interest to NICHD.

It could provide the start of an information center in the field of adult development and senescence so as to facilitate exchange of services with the National Clearinghouse for Mental Health Information that has contracted for abstracts in the field of mental retardation. This exchange of services would prevent duplication of abstracting and indexing of NIH. The services exchanged would include indexed abstracts in the field of adult development and senescence, bibliographies, and answers to questions in both subject areas.

These funds could permit a start toward cooperation with the NLM in completing their coverage (estimated now to be 15 to 50 percent) of the fields of interest to NICHD.

There is no need for studies of user needs since these are being and have been studied by other organizations including the Department of Defense.

The goal of the public information activities in NICHD is to inform the public of the results of their investment in this research organization, of plans for the future, and of current research. This information will aid in continuing public support of the program of the new Institute.

The Institute is planning to hold conferences of leading medical men and scientists in the fields of reproductive biology, perinatal biology, growth and development (from infancy through adolescence), adult development and senescence, mental retardation, developmental pharmacology, congenital malformations, human communications, for development of microthesauri in each of these areas, and for communications development in the fields of NICHD. The conference will reveal the latest concepts and gaps in knowledge. They will promote needed research programs and come up with microthesauri for indexing. There will be 15–20 conferences held in fiscal year 1965.

Field studies, 20 positions, $935,000 increase

Epidemiology and biometry, 20 positions, $935,000 increase

Personnel compensation	$87,600
Other objects	58,400
Contracts	789,000

The NICHD will make determined efforts to secure more adequate statistics on the incidence and distribution of specific childhoood health problems such as: Infant mortality, prematurity, mental retardation, congenital malformations, and uniquely informative disorders such as progeria (prococious) aging. Through epidemiologic and statistical studies of these problems important leads as to their causes can be obtained. In order to accomplish these objectives, the NICHD would initiate a direct operation to:

(*a*) Encourage complete reporting, so that statistics may more nearly reflect the true prevalence, and so that additions to the statistics may more nearly reflect the true incidence;

(*b*) Seek to improve hospital and clinic records so that the causes and characteristics may be studied more easily;

(*c*) Use common definitions and standardize recording of essential information, so that data from different States can be more meaningfully compared or pooled in an effort to arrive at national statistics;

(*d*) Disseminate statistics so that data may be readily available to all who are interested in childhood health problems.

Contract funds could be used for retrieving data from records such as are available in existing longitudinal growth and development studies and having them put on punchcards and later on tape for data analysis.

Training activities, 12 positions, $100,000:

Personnel compensation	$52, 000
Other objects	48, 000

The existing shortage of scientific manpower in the fields of mental retardation, pediatrics and obstetrics, plus the prediction of an even greater shortage in the future necessitates a major effort to increase and improve every facet of the training area. For this reason, NICHD proposed to establish in 1965 a child health and human development career program primarily designed to provide the Public Health Service with an adequately trained pool of career officers in these fields. This program would provide cross-disciplinary training such as pediatric training for neurologists, behavioral science training for pediatricians, and combined training in obstetrics and pediatrics for individuals undertaking research in the perinatal period at both governmental and nongovernmental facilities. The initiation of short-term courses of a specific technical nature is also considered an important adjunct to this program.

Review and approval, 6 positions, $67,000 increase:

Personnel compensation	$26, 000
Other objects	41, 000

This activity provides for our National Advisory Health Council, for special consultants on the training and other child health programs, and for the Institute staffs which review, analyze, and process research fellowships and training grant applications.

Attachment A

MAMMALIAN DEVELOPMENTAL BIOLOGY UNIT

Temporary construction, $150,000

This structure would serve as a temporary laboratory and housing area for research laboratory animals.

Permanent construction (planning), $225,000

This facility would serve multiple purposes: (1) a mammalian breeding and caging facility, with a provision for nurseries; (2) an area designed for general purpose research laboratory space; and (3) a service area including space needed for surgical and obstetrical procedures, treatment rooms, drug room, receiving room, locker, and office space. When completed, it would replace the aforementioned temporary structure. The total estimated cost, including planning, would approximate $3,225,000, and would be located at either the NIH farmsite or another suitable area.

NATIONAL CANCER INSTITUTE

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	Professional judgment budget
1. Grants:			
Research	$60,902	$62,384	$72,184
Fellowships	3,942	3,942	3,942
Training	8,932	9,000	9,000
Carcinogenesis resource operations grants (or contracts)	0	0	15,000
Total grants	73,776	75,326	100,126
2. Direct operations:			
Research	18,087	18,596	19,396
Collaborative studies	41,174	44,184	55,184
Review and approval of grants	1,920	1,979	2,200
Program direction	860	877	1,000
Total direct operations	62,041	65,636	77,780
Total estimate	135,817	140,962	177,906

1. GRANTS, INCREASE OF $24,800,000

Research, increase of $9,800,000

Regular program, increase of $8,300,000.—This budget would pay the approved grants recommended for payment by the National Advisory Council. The estimate provides for the same amount of new grants that will pass the Council in fiscal year 1964 plus $3 million in approved but unpaid grants carried over, including amounts for programed chemotherapy grants.

Childhood leukemia, increase of $1,500,000.—A result of treatment with research drugs is producing longer and longer periods of remission. In order that these children do not deprive other leukemic children of valuable hospital bed space, it is advisable that they be kept outside the hospital but near the clinical research unit for followup. They must be close to a parent or guardian and be provided with board and room and education. This sum would provide for five small units for followup research and permit more research in the still very ill.

Carcinogenesis, increase of $15 million

The field of carcinogenesis has been a neglected field except in viral carcinogenesis where research has been supported rather well in a number of facets. This is not the case in chemical carcinogenesis. The problem of exposure through pesticides, tobacco, chemicals met by the public in day-to-day life is a serious one. Facilities and certain skills are scarce. This amount would provide for grants to nonprofit institutions who would contract for work they were not equipped to do or the National Cancer Institute would supplement nonprofit resources through contract to extend the operating potential of nonprofit institutions. If this amount were available it would be essential that funds be available for at least 2, and hopefully, 3 years to provide assurance of funds during development.

2. DIRECT OPERATIONS, INCREASE OF $12,144,000

Research, increase of $800,000

Leukemia treatment units, $300,000.—This amount would be used for a unit similar to that described above under grants, for the National Cancer Institute's clinicians who have pioneered in certain aspects of leukemia research.

Instrumentation, $500,000.—The National Cancer Institute has been supporting development of instruments in blood separation and high-speed centrifuges which offer great promise for acceleration of progress in leukemia, virus and studies of cell components. This amount would be used for acceleration of this work.

Collaborative studies, increase of $11 million

Biometry and epidemiology, $1 million.—Epidemiology and biometric studies are becoming of increasing importance in such things as studies of micro-epidemics of leukemia. They will become crucial if a virus-leukemia link is found.

Multipurpose facility, $10 million.—The National Cancer Institute is prepared to operate a facility to concentrate on a broad field of carcinogenesis and chemotherapy and including instrumentation, virus and tissue culture, production, etc. This was commented on by the committees last year. These funds, if appropriated, should be available for 3 years during the startup period to assure the contractor (who would be investing large sums of money), of continuity of program.

Review and approval and program direction, increase of $344,000

These increases would provide staff, travel, and related costs necessary to carry out the program expansion referred to above.

Multiple-year financing

If increased funds for the carcinogenesis or the multipurpose facility were provided, the language of the act should be changed to provide that $25 million of the appropriation would be available for 3 years. This multiple-year financing would be necessary (1) for the carcinogenesis resource operations activity to enable nonprofit institutions or the Institute to provide for complex facilities in the study of chemical carcinogenesis; (2) for collaborative studies activity to enable the Institute to operate a multipurpose facility for studies in carcinogenesis and chemotherapy, including instrumentation, virus, tissue culture, and production.

A key feature in the above-mentioned multiple-year financing is that both programs would involve substantial investment by the contractor in order to provide the complex facilities and accomplish the broad program objectives. The contractor would have to be assured of continuity of program. This assurance would be more evident if financial support were available for 2 or 3 years.

NATIONAL INSTITUTE OF MENTAL HEALTH

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	Professional judgment budget
Grants:			
(*a*) Research	$66,010	$76,495	$76,495
(*b*) Fellowships	7,788	8,057	8,057
(*c*) Training	65,168	73,213	73,213
(*d*) State control programs	10,950	6,750	6,750
Direct operations:			
(*a*) Research	10,755	11,203	11,203
(*b*) Collaborative studies	3,979	3,986	3,986
(*c*) Training activities	1,054	1,088	1,088
(*d*) Professional and technical assistance	3,982	4,224	4,224
(*e*) Review and approval of grants	3,181	3,264	3,264
(*f*) Program direction	625	637	637
Total estimate	173,492	188,917	188,917

NATIONAL INSTITUTE OF DENTAL RESEARCH

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	1965 professional judgment budget
Grants:			
Research	$8,898	$9,415	$13,238
Fellowships	1,191	1,199	2,175
Training	4,476	4,708	5,250
Total grants	14,565	15,322	20,663
Direct operations:			
Research	3,286	3,482	4,594
Collaborative studies	565	565	1,065
Review and approval	533	554	719
Program direction	191	212	279
Total direct operations	4,575	4,813	6,657
Total obligations	19,140	20,135	27,320

The professional judgment of funds that could be effectively applied to this appropriation exceeds the President's budget by $7,185,000. This excess could be used as follows:

1. Grants, increase of $5,341,000

A. Research, increase of $3,823,000.—The increase would provide additional support in the following fields of research:

1. Congenital anomalies	$500,000
2. Periodontal disease	300,000
3. Adhesive restorative dental materials	750,000
4. Dental caries	500,000
5. Calcification	750,000
6. Other areas	473,000
7. Program development grants	250,000
8. General research support	300,000
Total	3,823,000

These include competing continuations, supplementals, expected backlog of approved projects from 1964, and estimated new approvals.

B. Fellowships, increase of $976,000.—This increase would provide $600,000 to support approximately 70 additional fellowships in the regular programs, and $376,000 to support approximately 20 additional research career awards.

C. Training, increase of $542,000.—The increase would be used primarily to establish 10 new programs in certain areas needing additional emphasis such as metallurgy, anthropology, crystallography, and electron microscopy, all of which represent "shortage areas," and would be used to support 50 additional trainees, bringing the National Institute of Dental Research training program up to the level of approximately 520 active trainees.

2. Direct operations, increase of $1,844,000

A. Research, increase of $1,112,000.—Of this increase, $20,000 would be provided for 2 additional positions in the Information Office to more adequately meet the need for improved communications related to a nationwide information program necessary for the accomplishment of the objectives of the NIDR; $45,000 would be provided for 4 positions in the Research Services Section to provide additional centrally furnished research services related to the expanded laboratory areas; $42,000 would provide support for 3 additional positions in the microbiology program to expand research in the areas of investigations to test the concept of transmissibility and infectivity of dental caries, to analyze the ecologic and pathogenic characteristics of the causative organism(s), and to expand appplication of germfree techniques; $45,000 would provide support for 2 additional positions in the biochemistry program to expand research in the areas of mineral exchanges and metabolism specifically related to alveolar bone resorption in periodontal disease, and prenatal factors conducive to oral anomalies; $177,000 would provide support for 6 additional positions in the histology and pathology program to allow expansion in the areas of physical biology with special emphasis on crystallography, analytical microradiography, electron diffraction and cytochemical studies; $77,000 would provide support for 4 new positions in the biometric and epidemiological programs to further exploit leads developed in the course of surveys relating principally to nutritional influences on periodontal disease and physiology of fluorides; $214,000 would support 12 new positions for clinical and epidemiological research in the following areas principally conducted in field stations: (1) to better define the nature and character of leukoplakic lesions of the oral mucosa and to characterize the processes involved in their transition to malignant lesions, (2) to study the biochemical and metabolic behavior of streptococci recovered from early carious lesions and dental plaque in highly caries-active children available in the Boston area, (3) to exploit leads in caries and periodontal disease etiology derived from animal experimentation in our Bethesda laboratories, (4) to study genetic patterns of abnormalities of growth and development among American Indian population groups of varied ethnic backgrounds, and (5) to develop and direct a program in dental restorative materials. An additional $30,000 would provide increased data processing for the human genetics program. The remaining $462,000 represents an increase to the NIH management fund for centrally furnished services.

B. Collaborative studies, increase of $500,000.—This increase would provide $500,000 for the expansion primarily in our program on adhesive dental restorative materials.

C. Review and approval of grants, increase of $165,000.—This increase would provide $114,000 to support seven new positions in order to effect reorganization of the extramural programs branch to provide adequate services for the NIDR grants program. An increase of $51,000 represents payment to NIH management fund for centrally furnished services.

D. Program direction, increase of $67,000.—Of this increase, $55,000 would provide four new positions and allow for an extensive program in analysis and review of operations, and initiation of scientific and technical communications office to plan activities for the use of information derived from research and training activities, as well as from direct operations. An increase of $12,000 represents payment to NIH management fund for centrally furnished services.

NATIONAL HEART INSTITUTE

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	1965 professional judgment budget
Grants:			
Research	$78,990	$87,781	$105,735
Fellowships	6,207	6,207	6,207
Training	14,786	14,984	16,871
Total, grants	99,983	108,972	128,813
Direct operations:			
Research	11,248	11,545	12,233
Collaborative studies	1,972	1,951	2,739
Training activities	273	282	282
Review and approval of grants	2,138	2,207	2,385
Program direction	433	441	548
Total, direct operations	16,064	16,426	18,187
Total estimate	116,047	125,398	147,000

The professional judgment of funds that could be effectively applied to this appropriation exceeds the President's budget by $21,602,000. This difference could be used as follows:

1. Research grants, difference of $17,954,000

A. Continuation and supplementation of existing program, difference of $7,971,000.—These funds could be used to supplement existing grants to provide for the application of more sophisticated instrumentation in medical research and for improved disciplinary techniques. These factors, advanced instrumentation and major shifting in research disciplines, are very real considerations which until recently have not greatly influenced program needs. Now, because of technical progress, a sizable portion of appropriated funds could be used to support the expense of more refined and dependable approaches to research problems. This is true for the thousands of projects currently supported as well as for future requests.

B. New grants, difference of $9,983,000.—(*a*) Cooperative study of drugs and coronary heart disease, $2 million. This amount could be used to expand the initial group of 6 investigators to 30 additional clinical groups. This would provide enough subjects to make the study more statistically valid.

(*b*) Development of an artificial heart, $2 million. A Committee on Organ Replacement, working closely with the Associate Director for Program Planning and Scientific Information, is rapidly developing plans for cooperative studies for the development of an artificial heart. New awards are anticipated to be recommended by 1965 for this amount.

(*c*) Research in cigarette smoking, $2 million. It is established that male cigarette smokers have a higher death rate from coronary disease than nonsmoking males. The association of smoking with other cardiovascular disorders is less well established. The conclusion of the Surgeon General's Committee on Smoking and Health states: "Male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance." The amount proposed is for research as a result of this report.

(*d*) General research support grants, $1,158,000. This amount, consistent with the percentage of this program in relation to total research grant funds in the President's budget, would provide proportionate support for general research support grants in line with other grant amounts in the professional judgment estimates.

(*e*) Cardiovascular clinical research centers, $2,800,000. New program anticipated in 1965 is for support of the resource component of approximately 12–15 new program project grants. Included in this amount is $800,000 for supplemental applications to meet an increased cost for hospitalization and other expenses of the existing centers program.

(*f*) Scientific evaluation and planning, $25,000. This specialized amount could be used primarily for support of a variety of ad hoc advisory committees to explore and advise on areas where there has been a recognized need for research development and stimulation.

2. Training grants, difference of $1,887,000

The primary purpose of the proposed increase would be to raise the award level in the undergraduate program in 4-year schools of medicine from $25,000 to $40,000 and for 2-year medical schools from $15,000 to $25,000. A broadening of the scope of this program is considered desirable to fulfill the purpose for which it was originally intended. This need is evident not only because there is an inability to do as much today as 10 years ago with the same amount of money but also there are new needs created by clinical acceptance of procedures and techniques. This means people and facilities formerly supported on this program are now demanded for clinical service and new personnel and facilities could be developed in order to achieve further advances in research and training.

3. Direct operations, differences of $1,761,000

This amount, spread among a variety of direct operating activities, could be programed generally as follows:

To sustain the intramural research conducted in NIH facilities in Bethesda at its current level, $588,000. No mechanism exists, such as supplemental funds in the grants area, to provide for more expensive research techniques as these develop. More extensive use of instrumentation, of radioactive materials, of complex and synthesized drugs, of research animals, all have combined to aid the research worker in solving problems and finding new approaches to cardiovascular problems not possible a few years ago. These factors also make research more expensive.

To fabricate, equip, and maintain an anaerobic laboratory, one in which a pure helium atmospheric environment would permit studies of oxygen sensitive enzyme systems, $100,000. Such a laboratory, a first of its kind, has aroused great interest not only among cardiovascular scientists but also among scientists from other Institutes, particularly Cancer.

For expanded contract programs in the geographical disease activities of the collaborative studies area, particularly for elucidating etiological factors and the natural history of cardiovascular disease in epidemiological studies, $388,000.

In staff and contractual support of grants relative to an expanded research program in smoking and cardiovascular disease, $400,000. The possibility of developmental research through contracts, as the identification of active components of smoke having cardiovascular effects and tests for excretion products of smoking such as urinary metabolites, should be determined.

For review, approval, processing, and scientific and administrative management of the various grant programs, $178,000.

For program direction in the Office of the Director, National Heart Institute, particularly for program planning and scientific communication, $107,000.

4. Reimbursements to the NIH management fund have not been considered in this document beyond the level reflected in the President's budget.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	1965 professional judgment budget
Grants:			
Research	$74,244	$80,261	$80,261
Fellowships	3,979	3,979	6,900
Training	13,220	13,690	14,600
Total grants	91,443	97,930	101,761
Direct operations:			
Research	11,490	11,867	12,160
Collaborative studies	1,594	1,597	1,597
Review and approval	1,415	1,491	1,561
Program direction	283	291	336
Total direct operations	14,782	15,246	15,654
Total estimate	106,225	113,176	117,415

The professional judgment of funds that could be effectively applied to this appropriation exceeds the President's budget by $4,239,000. This excess could be used as follows:

Fellowships

This valuable program provides training in areas of Institute interest for which regular training centers are not established or are not feasible and is an established, important mechanism for providing research training and support to qualified individuals at all levels of experience.

Fellowship training support at adequate levels is absolutely essential to production of the clinical and laboratory investigators needed for real progress against disease. Recent years have brought new research assignments, and revived or stimulated interest in more traditional areas of Institute responsibilities. The many and varied categories of such responsibility could effectively employ a significantly greater number of investigators, with the required degree of research sophistication, than are presently available. A more effective Institute program of research training can be conducted if properly planned allowances for growth are permitted.

An additional amount of $2,921,000 could provide only an estimated 100 additional postdoctoral and special types: 80 research career development awards; and for higher costs in the research career awards program.

Training

The NIAMD training program, although developed under prevailing NIH training program objectives, has evolved a unique pattern which is characterized by its diversity. This is inherent in a program which is neither completely disease or anatomical-system oriented. The several categorical training programs; namely, arthritis, dermatology, diabetes, endocrinology, gastroenterology, hematology, metabolism, nutrition, orthopedics, renal disease, and urology, span a large segment of the total spectrum of medical research and research training. This diversity is attestation to the NIAMD's fulfillment of its role with a viable program responsive to new and additional training needs as they become apparent.

Additional centers in orthopedics and dermatology, and especially in the area of urology could be established in order to capitalize on current interest in these fields.

An additional amount of $910,000 could provide additional trainees within established training centers, an estimated 20 additional centers, and for additional individual grant costs.

Research

This item, amounting to $293,000, includes three positions and $133,000 for the establishment of a new section of chemical physics in the Laboratory of Physical Biology. The present scientific approach in this area is biologically oriented physical chemistry. The proposed section will round out this effort by providing theoretical physics involving knowledge of molecular structure, and particular sophistication in problems closely related to polymer chemistry.

The remaining $160,000 could be used for normal cost increases in materials, outside services, and equipment. The equipment item not only rises in cost each year due to normal price trends, but becomes increasingly expensive due to continual development of new and more complex types.

Review and approval

This item is for five positions and $70,000 for grants to scientific program directors. Recent emphasis has necessarily been in improvements in grants management involving, primarily, business-oriented personnel for budget and fiscal program aspects. It is now felt that additional professional scientific staff, as specialized program directors, could provide the most effective program leadership and direction.

Program direction

This activity, with a total of 21 positions, comprises the Director's immediate staff and is responsible for the overall direction and central servicing of all institute programs. The positions have been authorized in past year's appropriations. Funds amounting to $45,000 would provide support for three of the positions not previously utilized.

ALLERGY AND INFECTIOUS DISEASES

1965 Professional Judgment Budget

[In thousands]

	1964 estimate	1965 President's budget	Professional judgment budget estimate
Grants:			
Research	$38,239	$38,973	$54,185
Fellowships	2,976	2,976	5,000
Training	7,949	8,239	9,500
Total grants	49,164	50,188	68,685
Direct operations:			
Research	11,174	11,615	12,195
Collaborative studies	5,285	5,285	7,345
Review and approval of grants	995	1,047	1,112
Program direction	300	310	360
Total direct operations	17,754	18,257	21,012
Total estimate	66,918	68,445	89,697

The professional judgment of funds that could be used effectively if applied to this appropriation exceeds the President's budget by $21,252,000. This amount could be used as follows:

1. GRANTS, $18,497,000

A. Research grants, $15,212,000

1. *Regular program, $14,712,000*

Allergy, $4 million.—In terms of numbers of individuals incapacitated and the cost to the Nation in loss in productivity of otherwise able citizens, the magnitude of the allergy problem is comparable to other major debilitating diseases. To those chronically or recurrently afflicted allergies are as depressing, disabling, and frustrating as any other disease. Medically and economically the challenge is formidable. Our present inadequate state of the art in dealing with allergic problems is derived primarily from several fortuitous observations on the effects of certain drugs intended for other purposes.

This amount would provide for development of major new research programs specifically planned for the purpose of engaging promising younger medical scientists with adequate training in basic sciences to undertake a coordinated study of the underlying physiological, biochemical, endocrinological, cytological, pathological, and immunological mechanisms, which relate to the phenomena of hypersensitivity, autoimmunity, abnormal host response mechanisms and other manifestations of the allergic state. An integral component of this program would be a provision for the assessment and development of more effective means for study of the adverse reactions to powerful new drugs, particularly as they relate to the allergic responses.

Tropical medicine, parasitic, and related diseases, $3 million.—Many of the diseases which are termed "tropical" are present in or potential invaders into the temperate zones. Tropical animals harbor a large number of disease agents transmissible to man. Some of these are readily transported by flying insects, migratory birds, and man himself. Evidence indicates that secondary disease reservoirs in temperate regions are being established and replenished from the vast reserve in the tropics.

An adequate study of such infectious diseases requires investigations into the environmental factors such as climate, reservoir animals, vectors, as well as the host characteristics of man such as race, varying susceptibility, immunity, and other biologic factors.

Active programing should be carried out for long-term flexible support of research activities in laboratories of proven productivity.

Pharmacological studies, $2 million.—A most significant advance in the history of the treatment and control of a major infectious disease occurred in 1963 with the demonstration of chemoprophylaxis of smallpox in man.

The importance of this event can hardly be overstressed. The direct benefits to be derived greatly overshadow the research costs in terms of simplified control and the reduction to relative impotence of an extremely dangerous potential hazard.

The opportunity now presents itself for exploitation of an important new finding. The new knowledge to be gained in pursuing the conceptual leads that have resulted from this observation may be expected to provide insight into the practicability of chemoprophylaxis of the host of other known and suspected viral diseases.

Virology, general, $3 million.—Measured in terms of production of useful knowledge, the funds provided for support of virological research during the past decade have been well spent. In addition to greatly enhancing our capability to deal effectively with viruses as diseases producing agents, studies using their unique characteristics have given impetus to major advances in a number of related research studies including genetics, cell biology, immunology, molecular biology, and biochemistry. Additional funds would be used to sustain a reasonable growth potential of research in the many active programs that have been making significant contributions.

Other infectious diseases, $2,712,000.—Research into other disease areas such as mycotic (fungus) infections long have been supported at a minimal level. Little is known about treatment of the deep mycotic infections. More research in the whole area of fungal infections is needed and more applications are expected which should be supported.

2. *Special programs, $500,000*

Clinical research centers.—This Institute has initiated and is expanding its long-range program for the development and maintenance of clinical research in chronic disorders of the immune mechanisms including allergy, asthma, and a number of poorly defined illnesses that indicate hypersensitivity to internal and external stimuli. The advances made in tissue and organ transplantation, prove the absolute need for working with the immune reactions. Detailed study of these reactions will be undertaken primarily through clinical trials and long-term observations.

B. Fellowships, $2,024,000

The research fellowship program complements the research and training grants programs through provision of support of worthy investigators from the postdoctoral fellow through the established career research scientist.

These programs have experienced rapid growth and all indications point to a significantly greater number of new applications which are likely to be reviewed in 1965. This growth coupled with a significant annual increase in average salaries further complicates the projected funding of these programs.

Postdoctoral, $1,027,000.—This amount for postdoctoral fellowships would be applied to increase the level of stipends in previously recommended fellowships and to provide funds for new awards which are judged by review groups to be outstanding.

Special, $283,000.—The traditional purpose of the special fellowship is to provide opportunities for established investigators to develop new skills and competency in selected research areas. An increased number of these awards would permit the Institute to engage in an active recruitment program. Awards would be made to well-qualified clinicians who wish to pursue careers in teaching and research in clinical allergy and infectious diseases.

The special and postdoctoral fellowship categories support individuals who, at a later stage of development, compete in the research career programs.

Research career awards programs, $714,000.—The purpose of the research career program is to increase the number of stable full-time career opportunities for scientists of superior potential and capability in the sciences related to health. Therefore, the vast majority of research career awards and research career development awards are awarded with long-term implied moral commitments. Approximately 85 percent of the total awards made in 1963 carried recommendations through 1965. The average salary level for these awards is increasing significantly, and a budgetary increase would enable the Institute to meet these moral commitments and to make additional awards. Expansion in this program should not take place through the mechanism of curtailing expenditures in the postdoctoral and special fellowship programs because these programs constitute a pool from which candidates are drawn for the research career program.

C. Training, $1,261,000

The graduate training grant program of this Institute provides opportunities for highly qualified scientists to procure the background training and experience essential for the conduct of basic and clinical investigations in the laboratory and in the field.

Notable progress in such areas as allergy and related chronic disorders depends greatly upon the availability of trained research personnel. The demand for personnel has not been met effectively because of the rapid expansion in virology and immunology. Therefore, the NIAID training grant program has been geared toward providing trained personnel for areas which are rapidly expanding and which are of primary concern to this Institute.

The inability to deal effectively with a growing number of refractory bacterial diseases points up the need for more extensively trained research personnel. These ends could be accomplished through the provision of additional funds for the graduate training program.

Funds for initiating and sustaining five new interdepartmental research training programs in selected institutions to gain greater depth and increased capability in the long-range assault upon the allergic diseases are also requested in the budget category.

2. DIRECT OPERATIONS, 55 POSITIONS AND $2,755,000

A. Research, 19 positions and $580,000

Cancer virus studies, 7 positions and $310,000.—Scientists have demonstrated that certain viruses, some of which are responsible for relatively minor respiratory illness in man, cause tumors when injected into animals under certain conditions. While this discovery is assuming great importance in virus-cancer research, it is also stimulating a large number of difficult questions that should be answered, many of which have direct bearing on the use of live viruses in vaccine development and related work. An extended and completely new and imaginative application of research skills and techniques to the questions of cell metabolism and basic cell structure is needed to explain what appears to be the oncogenic response of some cells to a massive invasion of certain viruses. A reorientation of experimental approaches is necessary to demonstrate the possible virus causation of human tumors and to exploit the recent findings in studies of virus-caused tumors in animals. An increased program of attempts to produce such animal tumors with other human viruses is indicated. An extra dividend from such work would be the development of knowledge leading to possible means of detecting which of the hundreds of known human viruses are potentially oncogenic. If viruses do cause human tumors, then cancer control through prevention of infection with those viruses is not possible until the viruses responsible can be specifically identified. Expanded effort should be applied to studies designed to demonstrate the presence of viral genetic material integrated into a tumor cell's genetic structure. In these studies may lie the specific means of proving a causative relationship between a particular human virus and human tumors. Of the increase proposed to expand this work, $150,000 would provide extremely complex instrumentation; $100,000 for cell and tissue cultures; $60,000 to supplement existing staff with personnel having backgrounds in biochemistry and cell genetics.

Arthropod-borne viruses, 12 positions and $270,000.—A corollary to the recently rapid extension of knowledge on the nature of viruses has been an increasing awareness of the importance of the arthropod-borne ("arbor") viruses. These viruses not only create serious public health and socioeconomic problems in tropical areas but also produce diseases that attack both humans and animals in the temperate zones. Through research, new viruses are being added to the arthropod-borne group every year, and these viruses are being found on every continent. To cope with the problems presented by the arborviruses, a major research effort should be directed at such requirements as isolating and characterizing causal agents, determining modes of transmission, describing the epidemiology of agents with special reference to possible vectors and reservoirs, and acquiring more information about the clinical diseases.

Hemorrhagic fever is an outstanding example of this Institute's research activities in arthropod-borne infections. The limited field study of this serious virus disease conducted in Bolivia last year in cooperation with the Bolivian Ministry of Health is of great importance not only to Bolivia but probably also to other areas of South America. It may also be closely related to hemorrhagic fevers occurring in other parts of the world.

Through efforts directed toward this problem last year the virus has been isloated, its mode of transmission and its source are not specifically known, although it is presumed to be carried by arthropods from animal reservoirs. Experience in working with this dangerous virus confirms the need for improved facilities with positive safety features essential for employee protection. Four members of the research team working in Bolivia on this problem last year contracted the disease and had to be evacuated to the Gorgas Hospital in the Canal Zone. Each of the four was seriously ill.

Although this research is extremely important in itself, a small investment here carries an added benefit in advancing the cause of friendship with our Latin American neighbors. Hemorrhagic fever is a serious disease problem in several Latin American countries and, in our experience with Bolivia, help is gratefully received. When hemorrhagic fever strikes an area, it frequently wipes out whole families and may result in practically the abandonment of communities. Places in South America in which this disease occurs from year to year are unsuitable for the resettlement of populations moved from nonproductive areas in the Andes Mountains.

Improved facilities for field study and new and better protective laboratory and isolation facilities, air filtering equipment, and safe animal holding quarters are essential to research in hemorrhagic fever. Key professional and supportive staff of the Middle America Research Unit would be provided an increase of eight positions—mostly for field work. Personal service increase of $50,000; $90,000 for renovation and installation of equipment for isolation laboratories; and $30,000 for travel, supplies, and material for support of adequate field parties is needed for this work.

Viral encephalitis, an example of temeprate-zone diseases that are extensions of infections and parasitisms indigenous to the tropics, also require continued emphasis. The MARU staff has conducted pioneer studies in the occurrence in Panama of St. Louis encephalitis and equine encephalitis (Venezuelan and eastern types).

During an epidemic of Venezuelan equine encephalitis (VEE) in Panama, three MARU staff members contracted the disease, and another acquired laboratory infection with VEE virus. Studies of these illnesses provided new data on this disease, which resembles the encephalitides occurring from time to time in various areas of the United States. An increase of four positions and $100,000 would support the additional research which is imperative to supply answers to many questions on the ecology and possible strain variations of VEE and on the protection that naturally acquired VEE infestions may offer against other viral infections, particular eastern equine encephalitis.

B. Collaborative studies, 26 positions and $2,060,000

Vaccine development, 20 positions and $2 million.—Extensive research efforts are currently being conducted to develop vaccines for the prevention of acute febrile respiratory illness and the common cold. Intensive efforts to find the causative agents of these illnesses have resulted in the identification of over 120 different viruses, some 50 of which have been implicated as causing the more common respiratory illnesses; of these, at least 15 are known to cause 60 percent of the acute febrile respiratory diseases in hospitalized children. The goals of basic and epidemiologic research are being satisfactorily approached, but there remains a wide gap in the application of this knowledge in terms of the development of vaccines against respiratory disease. A modest program for respiratory vaccine development was begun during 1962 with a budget of $400,000 concentrating on the intermediate objectives of developing vaccines for control of acute febrile respiratory illness of the most vulnerable segments of the population—children, military groups, and the aged.

Recent investigations have demonstrated that an urgent need exists for further research on the role of some respiratory viruses as latent tumor-producing agents. A modest effort has been initiated with available resources to provide more information on this important problem, which has direct implications as regards the safety of all viral vaccines.

Institute scientists in the Laboratory of Infectious Diseases now provide a large measure of the laboratory and epidemiologic competence for technical direction of the vaccine development program. The program is, in part, dependent upon the scientific resources of the intramural research program for comprehensive technical liaison and collaboration with the contractors and for continuous scientific review of contract projects. With the expansion of the vaccine development program and as more experimental vaccines become available for testing, the involvement of the extramural scientists will increase; such an important program resources is deserving of support.

Related to the problem of respiratory disease, consideration is now being given to the initiation of projects for the development and improvement of tuberculosis vaccines, based on new advances in technology which indicate that this is now feasible. Consideration is also being given to the status of research in hepatitis and Bolivian hemorrhagic fever to determine if it is feasible at this time to develop methods for control of these diseases, following the same lines that have been established in the program for respiratory vaccines.

In order to sustain the growing momentum of this national research effort and for the Institute to provide the leadership for this effort, additional funds and personnel could be used during 1965. An increase of 20 positions and $2 million would provide for the expansion of research contract programs and for adequate technical and staff support of the program activities.

Research reagents, six positions and $60,000.—Studies on the relationship of viruses to human disease are rapidly expanding and receiving increasing emphasis in modern biomedical research. Accurate identification of viruses and antibody response in man and animals is an essential prerequisite to such studies; yet specific reagents have not been generally available through commercial or other sources. The research reagents program has been developed to meet this situation by providing research workers with a series of standardized reagents. It is expected that these will be endorsed by the World Health Organization and therefore insure comparability of virus identification all over the world. Although progress toward achieving these goals has been substantial in 1964, it has fallen short of expectations. By the end of the year, antigens and/or antisera will have been produced for about 30 human adenoviruses, about 80 enteroviruses, and 21 myxo and related viruses and the processing and testing of many of these reagents should be finished. Feasibility trials of antigen concentration and immunization of horses to some 30 virus types are underway. A repository and distribution facility has been established and is being activated. Support has been given to regional laboratories equipped to give expert consultation service in the identification and characterization of viruses.

A program for production and evaluation of several standard ragweed allergen fractions and their corresponding antisera has been mapped out, and award of production contracts is expected. An increase of six positions and $60,000 would permit more adequate staffing in the intramural area to provide professional contract guidance and the needed laboratory support for continued quality control through specialized testing and production of seed stocks. It would also provide additional professional and clerical help in the branch office for new programs such as allergen standardization and for improved reference reagents. Somewhat increased support would be given to regional laboratories to provide expert consultative service in the identification and study of virus isolates and in the development of improved methods of isolation and identification.

C. *Review and approval of grants, 10 positions and $65,000*

These increases would materially strengthen the managerial and administrative capabilities of the extramural program. Managerial staff increases would facilitate the comprehensive review of the business aspects of research and training grant applications and expenditure reports.

The difficulties in the administrative and clerical area result from increased workload in connection with the technical review and processing of research and training grant applications. This function has grown in volume and complexity without proportionate increases in staff.

D. *Program direction, $50,000*

The burden upon the program direction activity to provide services to the other activities of this Institute has increased in direct proportion to the expansion of the program responsibilities of each of the three major operating areas.

During the past years, due to the cost of promotions and within-grade increases, the "Other objects" funds have been completely depleted, and it has not been possible to utilize five of the available positions. An increase of $50,000 could be used to reinstate these positions and to restore minimal "Other objects" support.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

1965 PROFESSIONAL JUDGMENT BUDGET

[In thousands]

	1964 estimate	1965 President's budget	Professional judgment budget
Grants:			
Research	$52,104	$56,955	$67,360
Fellowships	1,960	1,960	3,468
Training	14,382	14,751	15,410
Total grants	68,446	73,666	86,238
Direct operations:			
Research	7,252	7,549	7,750
Collaborative studies	5,146	5,056	5,791
Training activities	65	65	75
Review and approval of grants	1,651	1,710	1,760
Program direction	374	382	442
Total direct operations	14,488	14,762	15,818
Total obligations	82,934	88,428	102,056

A. *Research grants, $10,405,000*

	1965 President's budget	1965 professional judgment budget	Additional
Continuation and supplementals	$40,420,000	$45,100,000	+$4,680,000
New grants	7,790,000	11,000,000	+3,210,000
Additional indirect costs:			
20 percent	2,156,000	3,092,000	+936,000
25 percent	719,000	953,000	+234,000
Total regular programs	51,085,000	60,145,000	+9,060,000
General research support grants	4,625,000	4,625,000	------------
Scientific evaluation	45,000	90,000	+45,000
Categorical clinical research centers	1,200,000	2,500,000	+1,300,000
Total research grants	56,955,000	67,360,000	+10,405,000

The following programs could be supported with the amounts expressed in this professional judgment budget:

(1) Actual commitments to be carried forward from fiscal year 1964.

(2) The establishment of research information centers in communicative disorders and language and the structure of the human brain. Based upon recent experience with this type of activity, funds in excess of $600,000 could be applied in the initial year.

(3) More intensive research activity in cerebrovascular diseases with the purpose of accelerating activities aimed at improving the epidemiology and the diagnostic and therapeutic techniques for the treatment of stroke.

(4) Broadening the programing efforts in the evaluation of therapy and increasing the number of research teams involved in initiating controlled field trials for the treatment of neurosensory deficiencies.

(5) Special emphasis could be given to the development and evaluation of special research instruments, including the adaptation of industrial techniques to special problems of medical research.

B. Fellowships, $1,508,000

	1965 President's budget	1965 professional judgment budget	Additional
Postdoctoral	$385,000	$585,000	+$200,000
Research career awards	1,575,000	2,883,000	+1,308,000
Total fellowships	1,960,000	3,468,000	+1,508,000

An amount of $200,000 for 28 additional postdoctoral fellowships.

The importance of the career award program as a vital factor in maintaining the highest level of research accomplishment within the neurological and sensory disease sciences has become widely recognized. By providing full-time, stable research positions for proven scientist-investigators, the career award program is now contributing in an important way toward assuring that the highly trained scientist and scientist-clinician will be able to pursue his career as a teacher and independent investigator. Career awards are made only to outstanding scientists in important areas of neurological and sensory research.

An amount of $348,000 could be used for 15 additional RCA awards.

Through its training grant and fellowship programs, this Institute has helped provide young scientists with the disciplinary training needed in their preparation for careers in research and teaching in the neurological and sensory disorders. These young scientists have been superbly trained and need, at this point of their careers, to initiate the research for which they have been readied. The research career development award program provides for the establishment of the most promising of these young investigators within recognized teaching and research institutions.

An amount of $960,000 would support 60 additional RCDA awards.

C. Training, $659,000

	1965 President's budget	1965 professional judgment budget	Additional
Graduate training	$12,051,000	$12,710,000	+$659,000
Traineeships	2,560,000	2,560,000	0
Scientific evaluation	140,000	140,000	0
Total training	14,751,000	15,410,000	+659,000

By virtue of extensive programing efforts over the years, there have evolved many strong training centers, particularly in the clinical research disciplines of neurology, pediatric neurology, ophthalmology, and otolaryngology, with highly developed facilities and a full complement of able faculty and staff. These centers are now in a position to accommodate an increased number of scientist-physicians for training as teacher-investigators in the neurosensory fields.

In addition, this Institute could launch approximately 10 new training programs designed to prepare candidates for careers in research and teaching and organized community service in neurology, ophthalmology, and otolaryngology. In the preclinical sciences such as auditory physics, speech pathology, and sensory physiology, additional training programs at the postmaster and postdoctoral levels could be initiated.

An amount of $659,000 would be used to support these programs.

2. DIRECT OPERATIONS

The professional judgment budget for direct operations exceeds the President's budget by $1,056,000. Following is a distribution of this estimate by activity:

A. Research, $201,000

Of this increase, $151,000 would support 14 new positions for expanded research in medical and surgical neurology, biophysics, molecular biology, and neuropathology; $50,000 could be used for expanded instrumentation and service contracts.

B. Collaborative studies, $735,000

Perinatal Research Branch, $300,000.—This amount would include $100,000 and 10 new positions for the support of additional professional personnel for the vital analysis of data for this project. The amount of $200,000 could be utilized for increased contracting for research, development, and production of antigens, and for the development of instruments and techniques for biologic pattern data processing.

Biometrics, $200,000.—An amount of $100,000 and 10 new positions could permit the expansion of blindness and deafness registries under the model reporting area. Included also would be expanded biometric research studies in etiological investigations of congenital deficits of neurologic origin; $100,000 could be used for contracts to study the neurologic and sensory effect of smoking and the association between perinatal factors and congenital deafness.

Epidemiology, $100,000.—This amount could support five new additional positions for expansion of the amyotrophic lateral sclerosis survey in the Carolina Islands, and the clinical, pathological, epidemiological, and genetics investigations in Guam. Contractual studies on the toxicity of the cycad nut, and other botanical material, also could be supported.

Special projects, $60,000.—This amount could support five new positions for developing programs in evaluation of therapy, instrumentation, and other programed efforts. The funding of these would be from research grant funds, either as grants, or by transfers to direct operations, for use in contracts.

Special disorders of CNS, $75,000.—Of this amount, $50,000 and five new positions could be used to expand current studies on the effects of viruses on the central nervous system, especially in our temporary laboratories with Department of Interior's Patuxent Wildlife Research Center. The amount of $25,000 could be used for contracts to infect other animals, primarily monkeys in related studies.

C. Training, $10,000

This amount could support additional short- and long-term programs to train personnel in particular skills necessary to carry on research and technical projects.

D. Review and approval of grants, $50,000

This amount could support five new positions for the programing and analysis essential to the management of this program.

E. Program direction, $60,000

This amount could support five new positions for program analysis and development and for communications.

DESCRIPTION OF EACH NIH GRANT PROGRAM

REGULAR RESEARCH GRANTS

1. *Purpose of program.*—To provide grant support of research in health, medicine, and allied fields with the major objectives (1) of expanding medical and biological research activities in universities, hospitals, laboratories, and other public or private institutions and (2) of stimulating new investigations in fields needing exploration. The grant ranges from support of smaller, discrete, and circumscribed projects, which are defined as project grants, to support of

broad programs which integrate the research interests of several investigators, and which are called program project grants.

2. *Funds:*

1959 obligations	$139,629,000
1960 obligations	185,474,000
1961 obligations	240,607,000
1962 obligations	305,527,000
1963 obligations	353,102,000
1964 estimates	405,687,000
1965 estimates	440,182,000

3. *Present stage of development.*—The modest cancer grants program of 1938–45 of less than $100,000 annually changed in 1946 to a health, medicine, and related sciences program of $780,000. Steady annual increases since 1946 have produced the 1964 program of over $400 million. This will support more than 16,000 research projects conducted in almost 1,700 institutions throughout this country and abroad, and covering the full range of biological and related research. While the program continues in major part to support the ideas of investigators in the grantee institutions, a significant part of the grants provide support of programs reflecting initiative of NIH staff, such as cancer chemotherapy, psychopharmacology, and other collaborative programs.

4. *Plans for the future.*—The NIH believes that medical research should continue to expand as long as this country is faced with major crippling and killing diseases and conditions. Further, it believes that a number of factors contribute together to provide full assurance that substantial expansion can be effected. These factors include (1) a sharp expansion in the population base from which new M.D.'s and Ph. D's will be drawn, (2) a steadily rising college enrollment, (3) a significant percentage increase in graduate enrollment, and (4) improving educational opportunities for the more talented students, including both new medical schools and strengthened graduate and professional schools.

CLINICAL RESEARCH CENTERS

(Includes physical resources portions of program projects)

1. *Purpose of program.*—To provide grants to non-Federal research institutions for establishment of biomedical research centers of resources. These centers make possible the performance of meritorious and complex clinical investigation in the preclinical, clinical, and health-related sciences. They provide the opportunity for precise observations and controls which are essential to studies with patients. These centers administratively may be viewed as (*a*) categorical and (*b*) general. The categorical centers are supported by the appropriate Institute and are concerned primarily with a specific category or type of disease, such as heart disease or cancer, toward which the work of the particular Institute is oriented. In the general clinical research centers program, which is supported by the Division of Research Facilities and Resources, the research activity is not focused primarily on a single Institue-related category of disease, but rather on categories of disease and on numerous areas of preclinical and clinical science. All centers consist of discrete facilities with specialized bed arrangements, core laboratories, and trained personnel. They use a multidisciplinary approach where investigators with varied interests and techniques share the center's facilities. The centers are highly conductive to the advancement of knowledge regarding human health and disease.

2. *Funding of clinical research centers program* (*research center grants and physical resource component of program project grants*). (See attached worksheet.)

3. *Present stage of development.*—The earlier of the center's program, general clinical research centers, is now well underway with 69 centers having been awarded as of December 31, 1963. It is anticipated that awards will have been made to approximately 76 centers by the close of 1964. Important scientific accomplishments have already been noted.

Sixty-four categorical center grants had been awarded by the close of fiscal year 1963. It is anticipated that 13 additional awards will be made in 1964. As with the general clinical research centers program, the categorical programs have made important progress.

4. *Plans for the future.*—The 1965 President's budget will provide full continuation and supplemental support to the centers receiving awards in 1964 and provide new support for approximately five general and eight categorical centers.

FUNDING OF CLINICAL RESEARCH CENTERS PROGRAM

Research center grants and physical resource component of program project grants

[In thousands]

	Obligations, 1960	Obligations, 1961	Obligations, 1962	Obligations, 1963	Estimate, 1964	Estimate, 1965
Division of Research Facilities and Resources	[1] $2,993	[1] $8,000	$22,123	$17,374	$27,145	$27,684
Cancer	----	4,199	805	4,437	4,900	4,900
Mental	----	509	700	781	1,750	1,750
Heart	----	3,962	1,782	2,048	1,600	1,600
Dental	----	----	----	----	50	350
Arthritis	----	----	481	1,119	1,250	1,250
Allergy	----	----	500	237	1,000	1,000
Neurology	----	537	577	1,353	1,200	1,200
Total	2,993	17,207	26,968	27,349	38,895	39,734

[1] Includes obligations incurred against funds appropriated to the categorical institutes totaling $3 million.

SPECIAL RESOURCE CENTERS

1. *Purpose of program.*—To provide grants to non-Federal research institutions for support of specialized facilities that provide the basic tools of research and specialized services necessary for the support of institutional research programs. Such tools may consist of computers, highly trained technical staff, costly and complex instrumentation, or other aids to a large research operation.

2. *Funds:*

1962 obligations	$4,329,000
1963 obligations	6,117,000
1964 estimate	5,685,000
1965 estimate	8,200,000

3. *Present stage of development.*—Thirty-one grants had been awarded by the close of 1963. Ten additional awards are expected to be supported in 1964.

4. *Plans for the future.*—The 1965 President's budget will provide continuation and supplemental support for grants previously awarded.

PRIMATE RESEARCH CENTERS PROGRAM

1. *Purpose of program.*—To provide funds for the construction and basic operation of special research facilities or centers devoted to the advancement of all areas of knowledge on the biological characteristics of species structurally and physiologically similar to man throughout the entire lifespan of the subhuman primate. The objective is to acquire basic scientific information which will ultimately be useful in the prevention and treatment of human disease. Research facilities provided by this program are available to visiting scientists from all areas of this country and abroad.

2. *Funds:*

1960 obligations	$1,917,000
1961 obligations	7,000,000
1962 obligations	9,495,000
1963 obligations	4,444,000
1964 estimate	5,700,000
1965 estimate	7,000,000

3. *Present stage of development.*—This program calls for six regional and one national center, the latter committed to research on the primate itself. Initial awards have been made for all seven centers, each award providing two grants, one for total construction costs, and one for annual operating costs. The operat-

ing award is made each year after a detailed review of the proposed budget by the Division. One center has been completed and already has an on-going research program. The other six centers are in various stages of construction or final planning. During this interim period, directors of these centers are assembling corps staffs of scientists and technicians and, in temporary quarters, are conducting research using primates.

4. *Plans for the future.*—The requested funds in the 1965 President's budget will provide for the support, maintenance and some supplementation of the existing seven centers.

GENERAL RESEARCH SUPPORT GRANTS

1. *Purpose of program.*—To provide funds for the general support of the medical research and research training programs of institutions under conditions enabling the recipients to meet needs which could not be effectively met by other forms of support. The grants can be utilized for such purposes as capitalizing on emerging research opportunities, exploring new and unorthodox ideas, or stimulating and developing an overall research or research training program. The broad type of support made possible through these grants can enable an institution to achieve a better balance in their total research and training programs, and permit the recipient institutions to strengthen the administration of these programs under conditions and in directions of their own choice.

2. *Funds.*—The amount available for distribution to this program constitutes "such uniform percentage, not to exceed 15 per centum, as the Surgeon General may determine, of the amounts provided for grants for research projects for any fiscal year through the appropriations for the National Institutes of Health * * *" (Public Law 86–798).

1962 obligations	$20,000,000
1963 obligations	30,000,000
1964 estimate	35,000,000
1965 estimate	40,000,000

3. *Present stage of development.*—In 1964 general research support grants will provide support for 301 health professional schools, hospitals, research institutes, laboratories, centers and certain other nonprofit research organizations heavily engaged in heath related research.

4. *Plans for the future.*—The 1965 President's budget provides an increase over 1964 of $5 million. This will be used to permit the continuity of the 301 awards supported in 1964, and to support more then 50 additional institutions expected to merit eligibility by 1965.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

1. *Purpose of program.*—Research grants are awarded in this program to American universities to enable these universities to establish centers within both their own organizations, and in affiliate centers within foreign institutions to broaden collaborative research and research training in the biomedical fields.

2. *Funds.*—In 1961, this program was administered by the National Institute of Allergy and Infectious Diseases and supported by six of the Institutes plus the Division of General Medical Sciences. This same situation existed in 1962 except for the absorption by Allergy of the support of Heart and Arthritis Institutes. In 1963, the program was administered by the Office of International Research, OIR, part of the Office of the Director, NIH. In 1964, OIR was incorporated into the GRS appropriation.

1961 obligations	$1,937,000
1962 obligations	2,093,000
1963 obligations	2,483,000
1964 estimate	3,000,000
1965 estimate	3,000,000

3. *Present stage of development.*—The initial phase of the program devoted to the administratively complex task of developing foreign research facilities in collaboration with selected foreign universities and research institutions has been completed in each of the centers. All centers are now actively engaged in specific research projects.

A substantial portion of current research is focused upon the demography, epidemiology, and ecology of disease states of concern to the United States and the host nation. A multidisciplinary approach is being developed within the several centers to study more effectively the complex biomedical problems which prevail at the foreign sites. As a consequence, professional staffs are being developed and trained to investigate, through a selective amalgamation of basic science, clinical and public health research methods, not only tropical diseases, but a wide variety of other disease states which exist in these countries. Accordingly, the scientific programs in each center will progressively encompass the full spectrum of factors which directly or indirectly influence disease in the United States and abroad.

These programs include studies of social and other environmental factors which may be related to the development and persistence of acute and chronic diseases. The presence of distinct ethnic and demographic groups in foreign areas permit studies in depth of physical and biomedical factors which may be involved in racial susceptibility to disease.

In addition to the research in progress and being planned, each university is creating an effective training program for U.S. citizens at both the domestic and the oversea sites.

The five sets of cooperating institutions are as follows:

U.S. University	*Foreign Cooperating Institution*
Johns Hopkins University	All India Institute of Hygiene and Calcutta School of Tropical Medicine, Calcutta, India
University of California	Institute of Medical Research, Kuala Lumpur, Federation of Malaysia
Tulane University	Universidad del Valle, Cali, Colombia
Louisiana State University	University of Costa Rica, San Jose
University of Maryland	Institute of Hygiene and Lahore General Hospital, Lahore, West Pakistan

4. *Plans for the future.*—The 1965 President's budget provides $3 million for the continuation of this program.

RESEARCH CAREER AWARDS

1. *Purpose of the program.*—The purpose of this program is to provide increased numbers of stable career opportunities for scientists of superior potential and capability in the sciences related to health. The program includes young investigators who desire experience and further training in a productive research environment; scientists need experience to qualify for senior positions; and experienced investigators who are continuing to develop in productive careers of independent teaching and research.

2. *Funds.*—The research career award program was initiated in 1962 by merging, modifying, and absorbing the career research professorship components of the special fellowships and the senior fellowship programs. The growth of the program is shown in the figures below:

1962 obligations	$10, 012, 000
1963 obligations	14, 224, 000
1964 estimate	21, 167, 000
1965 estimate	22, 253, 000

3. *Present stage of development.*—Approximately 1,222 awards will be made in 1964. This exceeds the number awarded in 1963 by 329.

4. *Plans for the future.*—The 1965 President's budget will support this program at approximately its 1964 level.

SCIENTIFIC EVALUATION AND PLANNING GRANTS (CHAIRMAN'S GRANTS)

1. *Purpose of the program.*—To provide funds for the assistance of the national advisory councils through the technical and scientific review of grant applications, and through the support of meetings used for the exchange of scientific views.

2. *Funds:*

1961 obligations	$1,734, 000
1962 obligations	1, 244, 000
1963 obligations	1, 516, 000
1964 estimate	1, 687, 000
1965 estimate	1, 687, 000

3. *Present stage of development.*—Research grant applications are reviewed prior to submission to the advisory councils by the appropriate study section. Each of these sections has scientific competency in a particular field or research discipline, and each is comprised of outstanding civilian authorities in the relevant specialties. In the training area, individual applications are reviewed by groups called committees. Both the study sections and the committees are supported by chairman's grants.

In addition to financing these review activities, chairman's grants support an extensive group of ad hoc panels, symposia, conferences, and other types of meetings used for the exchange of professional views.

REGULAR RESEARCH FELLOWSHIPS

1. *Purpose of program.*—The purpose of the program is to support the training of qualified scholars for research and academic careers in the basic and clinical sciences in health and health-related fields and thereby to increase the number of trained research investigators and teachers in these fields.

There are three major categories of regular research fellowships: predoctoral, postdoctoral, and special.

Predoctoral fellowships are to assist individuals who have a bachelor's degree or equivalent in such training in the aforementioned fields as leads to a master's or doctoral degree. Postdoctoral fellowships are to support additional training for an individual who already has earned Ph. D., M.D., D.D.S., D.V.M., or equivalent degree. Special fellowships are to support groups of fellows who fit into one of the following: (1) those who have had at least 3 years of relevant research and/or professional experience after receipt of the doctoral degree; (2) those who have completed residency training requirements in a clinical specialty or its equivalent; and (3) those who need special training not met by other fellowship programs although they do not have a doctoral or equivalent degree.

2. *Funds*

Regular research fellowships

	Predoctoral	Postdoctoral	Special	Total
1959 obligations	$3,180,000	$3,728,000	$901,000	$7,809,000
1960 obligations	4,783,000	5,332,000	1,342,000	11,457,000
1961 obligations	5,200,000	6,857,000	2,188,000	14,245,000
1962 obligations	4,706,000	8,597,000	2,509,000	15,812,000
1963 obligations	7,869,000	8,626,000	3,642,000	20,137,000
1964 estimate	8,560,000	9,777,000	4,210,000	22,547,000
1965 estimate	9,295,000	9,054,000	3,847,000	22,196,000

3. *Present stage of development.*—Approximately 1,586 predoctoral fellows will be supported in 1964 for the general, mental, and dental programs. This is an increase of 53 over 1963. Approximately 1,349 postdoctoral fellows will be supported in 1964 by all the institutes. This is an increase of 139 over the 1963 level. Approximately 448 special fellows will be supported by all programs except neurology. This exceeds the 1963 support by 62.

4. *Plans for the future.*—The 1965 President's budget will provide support for approximately 3,285 individuals. This is a reduction from 1964 of approximately 12 predoctoral, 59 postdoctorals, and 27 special fellows.

INTERNATIONAL POSTDOCTORAL FELLOWSHIPS

1. *Purpose of the program.*—This program provides awards to promising foreign scientists to support their training in U.S. laboratories. Although it undoubtedly contributes to the improvement of foreign research capabilities, the objectives of the program are essentially domestic. One purpose, for instance, is to enrich the postgraduate biomedical training in this country by enabling foreign investigators to share their ideas and background with American colleagues. Another is to encourage foreign scientists to participate in research bearing upon American health problems. As this research is often continued and extended by the fellow upon return to his home country, additional oppor-

tunities are created for future collaborative efforts in research endeavors of importance to the United States.

2. *Funds:*

1959 obligations	$345, 000
1960 obligations	400, 000
1961 obligations	700, 000
1962 obligations	700, 000
1963 obligations	1, 198, 000
1964 estimate	1, 200, 000
1965 estimate	1, 200, 000

3. *Present stage of development.*—This program was established in Western Europe in fiscal year 1958 with 12 countries particpating. Plans were made at that time for an orderly increase in the number of participating countries based on research potential and likelihood that returning fellows would use training in the United States. The increase in the number of participating countries has progressed according to schedule as follows: 1959, 30; 1960, 36; 1961, 40; 1962, 41; 1963, 41; and in 1964 an estimated 41. In 1964, 140 fellows will be supported, the same number as in 1963.

4. *Plans for the future.*—A new policy established by the Office of International Research will limit most candidates, in fiscal year 1965, to a maximum 6 months' extension of fellowship tenure. It is hoped this policy will release more funds for appointment of new fellows. It was concluded, after much deliberation and with the supporting recommendation of the International Fellowship Review Panel, that it would be preferable to support a larger number of scientists to shorter fellowship terms rather than continue the previous liberal policy which permitted fellowship tenure of 2 year or occasionally longer, resulting in the appointment of fewer first-year fellows.

TRAINING GRANTS

1. *Purpose of program.*—To provide grant support of training in specified aspects of health, medicine, and allied fields with the major objectives of (*a*) insuring an adequate supply of competent research manpower, (*b*) alleviating critical shortages of professional personnel in certain areas affecting research teaching and service, and (*c*) facilitating within the student bodies of health-related professional schools the development of knowledge about special areas of disease that have particular significance. The training grant fulfills a dual function. Its funds underwrite certain expenses related to the specific training mission, including the provision of stipends to individuals selected for that training except in (*c*) above. It also serves to create and maintain an atmosphere essential to the training by providing a focal point for the specific discipline or disease within the training institutions.

2. *Funds:*

1959 obligations	$49, 812, 000
1960 obligations	74, 673, 000
1961 obligations	109, 928, 000
1962 obligations	114, 585, 000
1963 obligations	135, 502, 000
1964 estimate	168, 737, 000
1965 estimate	180, 047, 000

3. *Present stage of development.*—The National Institute of General Medical Sciences program is oriented toward disciplines which cannot be categorized according to specific diseases. The categorical programs are directed toward the prevention and cure of specific categories of diseases for which the Institutes other than NIGMS have assigned responsibilities. NIGMS support is provided through awards of fellowships and training grants which support the training of both predoctoral and postdoctoral trainees in the basic sciences. The categorical institutes utilize the same forms of support but the primary emphasis of their training programs is the predoctoral training of Ph. D.'s, M.D.'s, D.D.S.'s, D.V.M.'s, etc., to provide the blend of specialized research and clinical training that is essential for careers of research investigations and teaching in the health sciences.

4. *Plans for the future.*—The recruitment and training of scientists in the fundamental, biological, and medical sciences are required as part of the general

effort to expand the scientific competence of the Nation. Indeed, the key to the biological research anticipated in the future lies in the provision of trained manpower adequate in both quantity and quality. Accordingly, the factors cited in support of an expanded research grant program substantiate the necessity for increased training activities. In addition, increased needs for teachers and for personnel for medical services generate supplemental needs for training in specialized fields. The NIH training grant program is an integral and indispensable part of a total national effort to fulfill these needs. In terms of institutional objectives, the training grant is a uniquely valuable means of integrating efforts to deal with specific diseases or discipline problems. Although the characteristics of the program will change in response to changing requirements, such as the emerging needs to recruit scientists at the undergraduate level and to intensify programs for the training of technicians, the basic objectives of the programs will remain constant, and the attainment of these objectives will require an orderly annual expansion of expenditures.

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Capt. Thomas E. Cone, U.S. Navy, retired, 4925 Butterworth Place NW., Washington, D.C.

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Dr. R. Lee Clark, Jr., (65), director and surgeon in chief, University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Tex.

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Dr. A. McGehee Harvey (65), professor of medicine, Johns Hopkins Hospital, Baltimore, Md.

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Dr. J. Walter Wilson (64), professor of biology, Brown University, Providence, R.I.

EX OFFICIO MEMBERS

Dr. Lyndon E. Lee, Jr., Chief, Extra-VA Research Division, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Alternate for—

Dr. Joseph H. H. McNinch, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Brig. Gen. Joe M. Blumberg, Medical Corps, U.S. Army, Director, Armed Forces Institute of Pathology, Washington, D.C.

Alternate for—

Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary of Defense for Manpower, Department of Defense, Washington, D.C.

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Mr. Armand Gilinsky (64), Gilinsky & Mishkin, 122 East 42d Street, New York, N.Y.

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Mr. Mike Gorman (65), executive director, National Committee Against Mental Illness, 1028 Connecticut Avenue NW., Washington, D.C.

Dr. George C. Ham (65), professor and chairman, Department of Psychiatry, University of North Carolina, Chapel Hill, N.C.

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Dr. George Tarjan (64), superintendent and medical director, Pacific State Hospital, Box 100, Pomona, Calif.

Senator Robert D. Williams (66), the senate, California Legislature, State Capitol, Sacramento, Calif.

Dr. Robin M. Williams, Jr. (67), professor of sociology, Department of Sociology, Cornell University, Ithaca, N.Y.

Dr. Cecil L. Wittson, 66), chairman, Department of Neurology and Psychiatry, University of Nebraska, Omaha, Nebr.

Dr. Dael Wolfle (64), executive officer, American Association for the Advancement of Science, 1515 Massachusetts Avenue NW., Washington, D.C.

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Dr. A. Baird Hastings (64), Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, Calif.

Dr. John B. Hickam (67), professor and chairman, Department of Medicine, Indiania University Medical Center, Indianapolis, Ind.

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Dr. Champ Lyons (65), chairman, Department of Surgery, Medical College of Alabama, Birmingham, Ala.

Dr. Emanuel M. Papper (66), professor and chairman, Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, New York, N.Y.

Mr. William F. Poorman (64), president, Central Life Assurance Co., 611 Fifth Avenue, Des Moines, Iowa.

Dr. Paul W. Sanger (67), Doctors Building, 1012 Kings Drive, Charlotte, N.C.

Dr. Eugene A. Stead, Jr. (64), chairman, Department of Medicine, Duke University Medical Center, Durham, N.C.

Dr. Steward G. Wolf, Jr. (65), chairman, Department of Medicine, School of Medicine, University of Oklahoma, Oklahoma City, Okla.

EX OFFICIO MEMBERS

Dr. William B. Tucker, director, Pulmonary Disease Service, Veterans' Administration, Washington, D.C.

Alternate for—

Dr. Joseph H. McNinch, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Col. Herbert W. Coone, U.S. Air Force, Medical Corps, Chief, Consultants Division, AFMSTC, Office of the Surgeon General, Department of the Air Force, Washington, D.C.

Alternate for—

Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary for Manpower, Department of Defense, Washington, D.C.

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NATIONAL ADVISORY DENTAL RESEARCH COUNCIL

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Dr. Stephen P. Forrest (64), dean, School of Dentistry, St. Louis University, St. Louis, Mo.

Dr. Lewis Fox (66), dean, School of Dentistry, University of Connecticut, Storrs, Conn.

Dr. Laurence D. Haskew (67), vice chancellor, developmental services, University of Texas, Austin, Tex.

Dr. Maynard K. Hine (67), dean, School of Dentistry, University of Indiana, 1121 West Michigan Street, Indianapolis, Ind.

Dr. Andrew D. Holt (66), president, University of Tennessee, Knoxville, Tenn.

Dr. J. J. Longacre (65), director, Cleft Palate Clinic, Children's Hospital, 2350 Auburn Avenue, Cincinnati, Ohio

Dr. Emory W. Morris (65), president and general director, W. K. Kellogg Foundation, Battle Creek, Mich.

Dr. Randall G. Sprague (67), professor of medicine, Mayo Foundation, University of Minnesota Graduate School, Rochester, Minn.

Dr. David Weisberger (64), professor of dental medicine, Harvard School of Dental Medicine, Boston, Mass.

EX OFFICIO MEMBERS

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Capt. Carl A. Ostrom, head, Professional and Dental Research Branches, Dental Division, Bureau of Medicine and Surgery, Navy Department, Washington, D.C.

Dr. Luther L. Terry (Chairman), Surgeon General, Public Health Service, Washington, D.C.

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The Right Reverend Angus Dun (retired) (64), 3315 Q Street NW., Washington, D.C.

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Dr. Clement A. Finch (66), professor of medicine, University of Washington, School of Medicine, Seattle, Wash.

Mr. Miles Fiterman (64), president, National Foundation for Research in Ulcerative Colitis, Minneapolis, Minn.

Dr. Thomas H. Hunter (66), dean, School of Medicine, University of Virginia, Charlottesville, Va.

Dr. Franz J. Ingelfinger (65), professor of medicine, Boston University School of Medicine, Boston, Mass.

Dr. Arnold Lazarow (65), professor and head, Department of Anatomy, University of Minnesota, Minneapolis, Minn.

Dr. William D. Robinson (67), chairman, Department of Internal Medicine, University Hospital, Ann Arbor, Mich.

Dr. Ethan A. H. Shepley (67), Shepley, Kroeger, Fisse & Shepley, St. Louis, Mo.

Dr. Cornelius H. Traeger (66), 799 Park Avenue, New York, N.Y.

Dr. Frank H. Tyler (67), professor of medicine, University of Utah College of Medicine, Salt Lake County General Hospital, Salt Lake City, Utah.

Dr. Alfred E. Wilhelmi (65), professor and chairman, Department of Biochemistry, Emory University, Atlanta, Ga.

EX OFFICIO MEMBERS

Dr. Solomon A. Berson, Chief, Radioisotope Service, Veterans' Administration Hospital, 130 West Kingsbridge Road, Bronx, N.Y.

Alternate for—

Dr. Joseph H. McNinch, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Lt. Col. Glen K. Arney, Acting Chief Medical Consultant, Directorate of Professional Service, Office of the Surgeon General, Department of the Army, Washington, D.C.

Alternate for—

Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of the Assistant Secretary of Defense for Manpower, Department of Defense, Washington, D.C.

Dr. Luther L. Terry (Chairman), Surgeon General, Public Health Service, Washington, D.C.

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

Dr. Norman F. Conant (66), professor of mycology and assistant professor of bacteriology, Duke University School of Medicine, Durham, N.C.

Mr. David C. Crockett (65), associate director, Massachusetts General Hospital, Boston, Mass.

Dr. Edwin H. Lennette (67), chief, Viral and Rickettsial Disease Laboratory, State of California Department of Public Health, 2151 Berkeley Way, Berkeley, Calif.

Dr. Clayton G. Loosli (66), dean, School of Medicine, University of Southern California, 2025 Zonal Avenue, Los Angeles, Calif.

Dr. Walsh McDermott (65), professor, Department of Preventive Medicine, Cornell University Medical College, 1300 York Avenue, New York, N.Y.

Dr. Arthur P. Richardson (68), dean, School of Medicine, Emory University, Atlanta, Ga.

Dr. Leon H. Schmidt (66), National Primate Center, University of California, Davis, Calif.

Dr. Laurence H. Snyder (65), Department of Genetics, University of Hawaii, Honolulu, Hawaii

Mr. Steven M. Spencer (67), Saturday Evening Post, 666 Fifth Avenue, New York, N.Y.

Dr. David W. Talmage (67), professor of medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, Colo.

Dr. George W. Wharton (68), chairman and professor, Department of Zoology and Entomology, Ohio State University, Columbus, Ohio.

EX OFFICIO MEMBERS

Dr. Robert I. McClaughry, director, Educational Services, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Alternate for—

Dr. Joseph H. McNinch, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Col. Adam J. Rapalski, Chief, Preventive Medicine Division, Department of the OSG, Room 2525 Main Navy Building, Washington, D.C.

Alternate for—

Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary for Manpower, Department of Defense, Washington, D.C.

Dr. Luther L. Terry (Chairman), Surgeon General, Public Health Service, Washington, D.C.

NATIONAL ADVISORY NEUROLOGICAL DISEASES AND BLINDNESS COUNCIL

Dr. Raymond D. Adams (65), chief of neurology service, Department of Neurology, Massachusetts General Hospital, Boston, Mass. (Lafayette 3–8200. Ext. 791).

Dr. A. B. Baker (66), professor and director, Division of Neurology, University of Minnesota, Minneapolis, Minn. (Federal 9–7311).

Dr. Bernard Becker (67), professor of ophthalmology, Department of Ophthalmology, Washington University School of Medicine, St. Louis, Mo. (Forest 7–6400, Ext. 891).

Dr. John E. Bordley (64), director, Department of Otolaryngology, Johns Hopkins Hospital, Baltimore, Md. (Orleans 5–5500, Ext. 774).

Dr. Paul C. Bucy (65), 251 East Chicago Avenue (suite 1230), Chicago, Ill. (Delaware 7–6500).

Mr. Irving E. Carlyle (67), attorney and counselor at law, Wachovia Bank Building, Winston-Salem, N.C. (725–1311).

Dr. V. Everett Kinsey (66), assistant director of research, Kresge Eye Institute, 690 Mullett Street, Detroit, Mich. (WO. 1–7926).

Dr. Horace W. Magoun (66), dean, Graduate Division, University of California, Los Angeles, Calif. (West Los Angeles, branch 2–8911).

Mr. Leonard W. Mayo (64), executive director, Association for the Aid of Crippled Children, 345 East 46th Street, New York, N.Y. (Oxford 7–3150).

Dr. H. Houston Merritt (64), dean, College of Physicians and Surgeons, Columbia University, New York, N.Y. (579–3592, Ext. 5244).

Dr. Clark H. Millikan (65), consultant in neurology, Mayo Clinic, Rochester, Minn. (282–2511).

Mrs. Collette (Hobart C.) Ramsey (67), president, the Deafness Research Foundation, 366 Madison Avenue, suite 1010, New York, N.Y. (Murray Hill 2–3737).

EX OFFICIO MEMBERS

Dr. Warren V. Huber, Chief, Neurology Division, Psychiatry and Neurology Service, Veterans' Administration, Washington, D.C. (Telephone: Code 148—Extension 2511)

Alternate for—

Dr. Joseph H. McNinch, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Dr. Paul J. Bittick (Lt. Col.) (MC) USAF, Chief, Neurology Section, Andrews Air Force Base Hospital, Washington, D.C. (Telephone code 185—Extension 8336)

Alternate for—

Dr. Shirley C. Fisk, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary of Defense for Manpower, Department of Defense, Washington, D.C.

Dr. Luther L. Terry (chairman), Surgeon General, Public Health Service, Washington, D.C.

NATIONAL ADVISORY COUNCIL ON HEALTH RESEARCH FACILITIES

Dr. Clark D. Ahlberg (1965), vice president of research and administration, Syracuse University, Syracuse, N.Y.

Mrs. Helen L. Curry (1964), 3408 Huntoon, Topeka, Kans.

Dr. Robert J. Glaser (1965), president, Affiliated Hospitals Center, 641 Huntington Avenue, Boston, Mass.

Dr. David R. Goddard (1966), provost, University of Pennsylvania, Philadelphia, Pa.

Dr. Richard A. Harvill (1966), president, University of Arizona, Tucson, Ariz.

Dr. Maxwell E. Lapham (1965), provost, Tulane University, 218 Gibson Hall, New Orleans, La.

Hon. Stephen L. R. McNichols (1967), Hilton Office Building, Denver, Colo.

Dr. Raymond J. Nagle (1965), dean, College of Dentistry, New York University, 421 First Avenue, New York, N.Y.

Dr. Stanley W. Olson (1967), dean, College of Medicine, Baylor University, Texas Medical Center, Houston, Tex.

Mr. Hamilton S. Putnam (1967), 18 School Street, Concord, N.H.

Dr. W. T. S. Thorp (1964), dean, College of Veterinary Medicine, University of Minnesota, St. Paul, Minn.

Dr. George A. Wolf, Jr. (1964), executive director and vice president for medical and dental affairs, Tufts New England Medical Center, Boston, Mass.

EX OFFICIO MEMBERS

Dr. Howard E. Page, National Science Foundation, Washington, D.C.

Alternate for—

Dr. Harve Carlson, National Science Foundation, Washington, D.C.

Dr. Luther L. Terry (Chairman), Surgeon General, Public Health Service, Washington, D.C.

APPROPRIATION HISTORY AND OBLIGATIONS, 1957–65

SUMMARY

	PHS estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
Total, operating accounts:							
1957	$134,755,900	$128,528,000	$126,672,000	$135,672,000	$183,154,000	$183,154,000	$169,801,000
1958	202,487,000	192,280,000	190,183,000	190,183,000	226,783,000	[1] 211,183,000	210,261,000
1959	[2] 229,424,000	212,931,000	211,814,000	219,383,000	320,577,000	294,383,000	285,315,000
1960	337,846,000	309,096,000	294,279,000	344,279,000	480,604,000	400,000,000	390,350,000
1961	446,832,800	410,073,800	400,000,000	455,000,000	664,000,000	560,000,000	[3] 545,616,000
1962	666,154,000	641,000,000	583,000,000	641,000,000	835,670,000	738,335,000	667,048,000
1963	885,314,000	855,000,000	780,400,000	840,800,000	900,800,000	880,800,000	751,442,000
1964	1,049,825,000	954,493,000	930,454,000	912,454,000	930,454,000	918,454,000	------------
1965	1,039,185,000	990,620,000	957,367,000	------------	------------	------------	------------

[1] In addition, $580,000 was transferred from "Grants to States for public assistance."

[2] Subsequent to 1958 Senate allowance this amount was increased to $234,971,000.

[3] Includes $12,139,000 transferred to "Construction of mental health-neurology research facility."

NOTE.—"Obligations" on all tables include rental payments made to GSA by transfer.

GENERAL RESEARCH AND SERVICES

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$11,944,000	$11,942,400	$11,922,000	$11,922,000	$12,122,000	$12,122,000	$12,001,000
1958	14,097,000	14,161,000	14,026,000	14,026,000	14,026,000	[1] 14,026,000	14,081,000
1959	26,220,000	17,774,000	17,766,000	17,742,000	32,552,000	28,974,000	28,957,000
1960	35,299,000	30,766,000	28,974,000	36,404,000	49,585,000	45,994,000	45,789,000
1961	52,711,100	47,266,100	47,260,000	52,660,000	104,405,000	83,900,000	83,572,000
1962	122,683,000	119,275,000	95,341,000	119,275,000	140,000,000	127,637,000	118,205,000
1963	161,851,000	150,300,000	147,826,000	155,826,000	161,826,000	159,826,000	139,525,000
1964	211,901,000	179,366,000	164,674,000	163,869,000	164,674,000	163,869,000	------------
1965	177,149,000	168,113,000	163,745,000	------------	------------	------------	------------

[1] In addition, $58,000 was transferred to this account from "Grants to States for public assistance."

BIOLOGICS STANDARDS

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1964	$4,838,000	$4,838,000	$4,787,000	$4,787,000	$4,787,000	$4,787,000	------------
1965	5,075,000	5,075,000	4,992,000	------------	------------	------------	------------

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

	PHS estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1964	($34,000,000)	($34,000,000)	($34,000,000)	($34,000,000)	($34,000,000)	[1]($34,000,000)	----------
1965	49,147,000	44,487,000	43,169,000	------------	------------	------------	----------

[1] Congress authorized the transfer of $34,000,000 from other NIH appropriations to establish the National Institute of Child Health and Human Development.

NATIONAL CANCER INSTITUTE

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$35,222,300	$32,875,700	$32,437,000	$34,437,000	$48,432,000	$48,432,000	$42,556,000
1958	51,608,000	47,314,000	46,902,000	46,902,000	58,543,000	56,402,000	55,454,000
1959	58,943,000	56,744,000	56,060,000	57,423,000	81,129,000	75,268,000	69,398,000
1960	81,864,000	80,232,000	75,218,000	83,308,000	110,203,000	91,257,000	85,030,000
1961	95,995,400	88,785,400	88,869,000	102,469,000	126,375,000	111,000,000	106,262,000
1962	129,519,000	125,672,000	117,167,000	125,672,000	160,000,000	142,836,000	118,117,000
1963	158,901,000	155,700,000	139,109,000	150,409,000	158,409,000	155,742,000	122,379,000
1964	154,999,000	145,706,000	145,114,000	144,340,000	145,114,000	144,340,000	------------
1965	146,898,000	145,058,000	140,962,000	------------	------------	------------	------------

MENTAL HEALTH ACTIVITIES

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$23, 939, 700	$21, 916, 200	$21, 749, 000	$23, 749, 000	$35, 197, 000	$35, 197, 000	$30, 274, 000
1958	39, 946, 000	36, 988, 000	35, 217, 000	35, 217, 000	43, 994, 000	[1] 39, 217, 000	39, 241, 000
1959	39, 718, 000	37, 895, 000	37, 788, 000	40, 397, 000	55, 896, 000	52, 419, 000	49, 889, 000
1960	58, 998, 000	53, 966, 000	52, 384, 000	60, 409, 000	79, 986, 000	68, 090, 000	67, 543, 000
1961	78, 693, 200	73, 610, 200	67, 563, 000	79, 863, 000	110, 800, 000	100, 900, 000	[2] 97, 191, 000
1962	95, 279, 000	92, 182, 000	88, 324, 000	92, 182, 000	125, 570, 000	108, 876, 000	108, 051, 000
1963	138, 652, 000	135, 800, 000	126, 899, 000	133, 599, 000	148, 599, 000	143, 599, 000	139, 517, 000
1964	206, 061, 000	193, 277, 000	190, 096, 000	177, 288, 000	190, 096, 000	183, 288, 000	-----------
1965	221, 291, 000	201, 504, 000	188, 917, 000	-----------	-----------	-----------	-----------

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[1] In addition, $114,000 was transferred to this account from "Grants to States for public assistance."
[2] Includes $5,139,000 transferred to "Construction of mental health-neurology research facility."

NATIONAL HEART INSTITUTE

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$22, 978, 500	$22, 863, 900	$22, 106, 000	$25, 106, 000	$33, 396, 000	$33, 396, 000	$32, 392, 000
1958	35, 822, 000	33, 815, 000	33, 436, 000	33, 436, 000	38, 784, 000	[1] 35, 936, 000	35, 973, 000
1959	[2] 34, 683, 000	34, 924, 000	34, 820, 000	36, 212, 000	49, 529, 000	45, 613, 000	45, 468, 000
1960	52, 911, 000	47, 671, 000	45, 594, 000	52, 744, 000	89, 500, 000	62, 237, 000	61, 565, 000
1961	69, 798, 700	65, 047, 700	63, 162, 000	71, 762, 000	125, 166, 000	86, 900, 000	86, 239, 000
1962	110, 205, 000	105, 723, 000	97, 073, 000	105, 723, 000	160, 100, 000	132, 912, 000	110, 899, 000
1963	155, 712, 000	148, 000, 000	126, 898, 000	143, 398, 000	149, 398, 000	147, 398, 000	104, 319, 000
1964	149, 185, 000	136, 300, 000	133, 624, 000	132, 404, 000	133, 624, 000	132, 404, 000	-----------
1965	132, 118, 000	128, 785, 000	125, 398, 000	-----------	-----------	-----------	-----------

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[1] In addition, $147,000 was transferred to this account from "Grants to States for public assistance."
[2] Subsequent to 1958 Senate allowance this amount was increased to $37,139,000.

NATIONAL INSTITUTE OF DENTAL RESEARCH

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$3, 237, 700	$3, 067, 500	$2, 971, 000	$3, 471, 000	$6, 026, 000	$6, 026, 000	$5, 949, 000
1958	6, 635, 000	6, 532, 000	6, 430, 000	6, 430, 000	6, 430, 000	[1] 6, 430, 000	6, 466, 000
1959	7, 719, 000	6, 481, 000	6, 359, 000	6, 543, 000	7, 923, 000	7, 420, 000	7, 405, 000
1960	9, 907, 000	7, 715, 000	7, 420, 000	9, 725, 000	10, 164, 000	10, 019, 000	9, 968, 000
1961	13, 803, 300	11, 996, 300	11, 204, 000	12, 604, 000	16, 710, 000	15, 500, 000	14, 616, 000
1962	15, 265, 000	14, 681, 000	13, 933, 000	14, 681, 000	20, 000, 000	17, 340, 000	15, 108, 000
1963	20, 017, 000	19, 700, 000	17, 199, 000	19, 199, 000	22, 199, 000	21, 199, 000	17, 451, 000
1964	23, 314, 000	20, 212, 000	19, 809, 000	19, 689, 000	19, 809, 000	19, 689, 000	-----------
1965	20, 943, 000	20, 290, 000	20, 135, 000	-----------	-----------	-----------	-----------

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[1] In addition, $50,000 was transferred to this account from "Grants to States for public assistance."

ARTHRITIS AND METABOLIC DISEASE ACTIVITIES

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$13,517,900	$13,481,600	$13,345,000	$13,845,000	$15,885,000	$15,885,000	$15,850,000
1958	18,027,000	18,024,000	17,885,000	17,885,000	23,548,000	[1] 20,385,000	20,480,000
1959	[2] 20,319,000	20,579,000	20,668,000	21,092,000	34,798,000	31,215,000	31,126,000
1960	37,014,000	32,564,000	31,215,000	37,790,000	51,200,000	46,862,000	46,182,000
1961	52,949,900	47,519,900	47,541,000	52,841,000	70,760,000	61,200,000	58,608,000
1962	77,783,000	73,661,000	68,740,000	73,661,000	90,000,000	81,831,000	78,956,000
1963	103,761,000	101,560,000	91,921,000	98,721,000	105,721,000	103,388,000	95,110,000
1964	124,579,000	115,759,000	114,717,000	113,679,000	114,717,000	113,679,000	----------
1965	121,595,000	117,119,000	113,176,000	----------	----------	----------	----------

[1] In addition, $97,000 was transferred to this account from "Grants to States for public assistance."

[2] Subsequent to 1958 Senate allowance this amount was increased to $21,929,000.

ALLERGY AND INFECTIOUS DISEASE ACTIVITIES

	PHS estimate to department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$10,994,200	$10,081,900	$9,946,000	$8,946,000	$13,446,000	$13,446,000	$13,418,000
1958	16,407,000	16,405,000	17,400,000	17,400,000	17,400,000	[1] 17,400,000	17,506,000
1959	21,044,000	17,663,000	17,593,000	17,997,000	26,500,000	24,071,000	24,039,000
1960	29,126,000	25,379,000	24,071,000	30,286,000	41,000,000	34,054,000	34,025,000
1961	38,477,100	35,462,100	34,739,000	38,439,000	48,234,000	44,000,000	43,780,000
1962	54,833,000	52,182,000	48,322,000	52,182,000	60,000,000	56,091,000	54,676,000
1963	64,262,000	64,155,000	59,342,000	62,142,000	68,142,000	66,142,000	62,382,000
1964	79,569,000	69,765,000	69,226,000	68,723,000	69,226,000	68,723,000	----------
1965	70,724,000	68,985,000	68,445,000	----------	----------	----------	----------

[1] In addition, $114,000 was transferred to this account from "Grants to States for public assistance."

NEUROLOGY AND BLINDNESS ACTIVITIES

	PHS estimate to Department	Department estimate to Bureau of the Budget	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation	Obligations
1957	$12,921,600	$12,298,800	$12,196,000	$14,196,000	$18,650,000	$18,650,000	$17,361,000
1958	19,945,000	19,041,000	18,887,000	18,887,000	24,058,000	21,387,000	21,060,000
1959	[1] 20,778,000	20,871,000	20,760,000	21,977,000	32,250,000	29,403,000	29,033,000
1960	32,727,000	30,803,000	29,403,000	33,613,000	48,966,000	41,487,000	40,248,000
1961	44,404,100	40,386,100	39,662,000	44,362,000	61,550,000	56,600,000	[2] 55,348,000
1962	60,587,000	57,624,000	54,100,000	57,624,000	80,000,000	70,812,000	63,036,000
1963	82,158,000	79,785,000	71,206,000	77,506,000	86,506,000	83,506,000	70,759,000
1964	95,379,000	89,270,000	88,407,000	87,675,000	88,407,000	87,675,000	----------
1965	94,245,000	91,204,000	88,428,000	----------	----------	----------	----------

[1] Subsequent to 1958 Senate allowance this amount was increased to $22,259,000.

[2] Includes $7,000,000 transferred to "Construction of mental health-neurology research facility."

HISTORY OF CONGRESSIONAL ACTION ON BUDGET REQUESTS FOR NIH

Year	Budget request			Appropriation		
	Obligational cash	Liquidating cash	Contract authority	Obligational cash	Liquidating cash	Contract authority
1932	$48,000			$48,000		
1933	48,000			48,000		
1934	54,775			54,775		
1935	50,000			50,000		
1936	64,000			64,000		
1937	64,000			64,000		
1938	464,000			464,000		
1939	515,000			515,000		
1940	587,750			707,000		
1941	712,120			711,000		
1942	705,000			700,000		
1943	1,278,270			1,278,270		
1944	1,291,000			2,555,020		
1945	2,835,000			2,835,000		
1946	2,078,000			3,414,700		
1947	10,799,500			[1] 8,125,448		
1948	22,403,000			28,876,000		
1949	45,701,460		$2,300,000	37,668,000		$10,300,000
1950	40,567,000	$3,900,000	3,595,000	50,167,000	[2] $4,925,000	15,425,000
1951	49,845,000	12,725,000		[3] 47,334,750	12,725,000	
1952	53,386,000	5,648,000		52,477,291	5,198,000	
1953	55,005,000			59,030,750		
1954	56,340,000			71,153,000		
1954 [4]	71,128,000			81,268,000		
1956 [5] [6]	90,023,000			98,458,000		
1957 [5]	[7] 126,725,000			183,007,000		
1958	190,183,000			211,183,000		
1959	211,814,000			294,383,000		
1960	294,279,000			400,000,000		
1961	400,000,000			[8] 560,000,000		
1962	583,000,000			[9] 738,335,000		
1963	780,400,000			880,800,000		
1964	930,454,000			918,454,000		
1965	957,367,000					

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[1] Includes $386,500 transfers.

[2] Not less than $3,000,000 was earmarked for liquidating cash; an additional $1,175,000 was used for that purpose.

[3] Excludes $3,216,250 rescinded.

[4] Excludes $131,000 for Gorgas Memorial Laboratory.

[5] Excludes $147,000 for Gorgas Memorial Laboratory.

[6] Includes $90,000 transfer.

[7] Includes $200,000 transfer from other appropriations.

[8] Includes $12,139,000 for construction of mental health-neurology research facility.

[9] Includes $1,000,000 for planning for a gerontological research facility; and $750,000 for modernization at the Rocky Mountain Laboratory, Hamilton, Mont.

NOTE.—Not all amounts in this table are comparable from year to year because of inconsistencies in the content of the appropriations. Prior to 1938 they exclude all salaries. Prior to 1943 they exclude all salaries other than those of employees of the National Cancer Institute. Prior to 1949 they exclude pay of regular corps officers. For 1948, 1949, and 1950 they include funds for support of narcotic hospitals at Fort Worth and Lexington which were subsequently transferred.

GENERAL RESEARCH AND SERVICES

WITNESSES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. CLINTON C. POWELL, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

DR. FREDERICK L. STONE, CHIEF, DIVISION OF RESEARCH FACILITIES AND RESOURCES

DR. CHARLES V. KIDD, ASSOCIATE DIRECTOR FOR INTERNATIONAL ACTIVITIES, NATIONAL INSTITUTES OF HEALTH

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
11 Personnel compensation:			
Permanent positions	1,865	2,330	2,631
Positions other than permanent	110	77	71
Other personnel compensation	56	82	82
Total personnel compensation	2,031	2,489	2,784
12 Personnel benefits	191	242	271
21 Travel and transportation of persons	388	563	575
22 Transportation of things	41	79	82
23 Rent, communications, and utilities	86	120	120
24 Printing and reproduction	8	22	22
25 Other services	3,455	1,498	1,505
Payment to National Institutes of Health management fund	807	819	844
26 Supplies and materials	58	109	108
31 Equipment	158	119	116
41 Grants, subsidies, and contributions	128,782	147,150	157,318
Subtotal	136,005	153,210	163,745
Deduct quarters and subsistence charges	2		
Total obligations	136,003	153,210	163,745

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	325	358	374
Full-time equivalent of other positions	17	13	12
Average number of all employees	266	308	337
Employees in permanent positions, end of year	302	338	354
Employees in other positions, end of year	48	12	22
Average GS grade	7.4	7.7	7.7
Average GS salary	$7,072	$7,610	$7,628

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	82,064	96,961	105,171
(*b*) Fellowships	13,327	14,507	14,965
(*c*) Training	33,391	35,682	37,182
Total, grants	128,782	147,150	157,318
2. Direct operations:			
(*a*) Collaborative studies	109	1,315	1,315
(*b*) International research	842	1,061	1,147
(*c*) Training activities	19	156	165
(*d*) Review and approval of grants	1,977	2,602	2,829
(*e*) Program direction	882	926	971
Total, direct operations	3,829	6,060	6,427
Total program costs, funded [1]	132,611	153,210	163,745
Change in selected resources [2]	3,392		
Total obligations	136,003	153,210	163,745
Financing:			
Comparative transfers to others accounts	3,434		
Unobligated balance lapsing	20,267	996	
New obligational authority	159,703	154,206	163,745
New obligational authority:			
Appropriation	159,826	163,869	163,745
Transferred to—			
"Operating expenses, Public Buildings Service" General Services Administration (76 Stat. 728)	−123		
"Salaries and expenses, Office of the Surgeon General" (42 U.S.C. 226)		−17	
"National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−9,646	
Appropriation (adjusted)	159,703	154,206	163,745

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[1] Includes capital outlay as follows: 1963, $76,000; 1964, $119,000; 1965, $116,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $639,000 (1963 adjustments −$35,000); 1963, $3,997,000; 1964, $3,997,000; 1965, $3,997,000.

STUDY OF THE NATIONAL INSTITUTE OF HEALTH

Mr. FOGARTY. The meeting will come to order. Dr. Shannon, I mentioned this study of the National Institutes of Health before. Will you give us just a brief statement on the reasons for this study?

Dr. SHANNON. Yes, sir. This is a Committee, the establishment of which was discussed, as I understand it, by Senator Hill.

These discussions took place at a time when the National Institutes of Health underwent a serious study by one of the Committees on Government Operations of the House. I have always felt that an objective and useful survey of our activities might pay more attention to the excellence of the program and to the impact of the program on the universities rather than concentrating on grants administration aspects of the program.

The President, in discussions with Dr. Wiesner at that time, in the presence of the Science Adviser, and later, the Chief of the Office of Science and Technology, decided to go ahead with the program and appoint a Committee during the spring and summer of last year, with the idea of getting underway the following fall. There was some delay in getting the Committee together. Actually, it was assembled for the first time for the first meeting in January.

The composition of the Wooldridge Committee includes both scientists and nonscientists. The nonscientists, however, are people from industry who, by virtue of their industrial contact, have experience with broad aspects of research and development. It was felt that this committee could best serve the public interest by evaluating the excellence of the program and the reasonableness of the tenets under which it operates.

One of the reasons that Dr. Wiesner and President Kennedy were very anxious to have the study, apart from the discussion that precipitated it, is that it was felt that here—in science—were a series of very large programs, financed mainly by the Federal Government, which present unusual and difficult problems of management. In order to determine whether in fact these programs are approaching their objectives, Dr. Wiesner in discussion with the President felt they would like to take the NIH as the first of a series of studies addressed to some of these broad issues.

Some of the other program areas considered relate to oceanography, material research, and the like. We have had one meeting with the Wooldridge Committee early this month, to discuss the generalities of the problems as we see them at NIH and to give them an orientation relative to NIH activity. They have developed a program that will assess both the substance and the administrative practices of the National Institutes of Health, both as viewed from Headquarters in the NIH, and as it operates within a number of university settings that are largely dependent on NIH grants for the integrity of their activity.

The teams that will study the institutional impact and the excellence obtained in the university will be technicians, or rather, scientists, who have been drawn from both physical and biomedical sciences so that they are in a good position to assess the excellence and pertinence of grants. It is hoped that these scientific teams will follow through in reports, so that quite apart from what we find in individual institutions, it will be possible to view a cross section of activity or view an entire area of science, such as biochemistry, biophysics, or the like. From this, we should see how our programs affect the university; how grant recipients perform; and finally, by disciplinary areas, the extent to which opportunities offered are being taken.

One of the groups came to NIH just yesterday for general briefing on NIH practices, before proceeding on to one of the universities. I think that the study will be objective; the individuals selected to head the studies; namely, the Committee, are not intimately involved with NIH. Generally, they have no prior contact with us.

I believe also that this will be constructive study; and in no sense purely expeditious, where anything is prejudged, in relation to what they are trying to do. I think, finally, that broad programs of medical research or oceanography or the like, will do well to have this type of external audit. So I may say that we are looking forward to a constructive report from the Committee.

General Research and Services

Mr. Fogarty. Who is going to justify "General research and services?"

Dr. Shannon. Well, Mr. Fogarty, in general research and services, we are presenting to you three general activities or three activities that are discreet entities within themselves, but are budgeted under that appropriation. If I may just outline each of these three areas, then I think we can break this into three discussions that Dr. Powell, Dr. Kidd, and Dr. Stone can handle.

GENERAL STATEMENT

I have a general statement that I would like, if I may, to submit for the record, and I will limit my remarks to a very brief introduction.

Mr. FOGARTY. All right. Go ahead.

(The Director's general statement follows:)

Mr. Chairman and members of the committee, this appropriation provides support for the general, noncategorical operating programs of the National Institutes of Health. These are the Institute of General Medical Sciences (formerly the Division of General Medical Sciences), the Division of Research Facilities and Resources, and the Office of International Research which until last year was represented as a part of my immediate office.

The 1965 request totals $163,745,000 compared to the 1964 operating level of $153,210,000, or an increase of $10,535,000. We have prepared a table which summarizes the relationship of the estimates for these three organizations to the standard budget structure. I believe it will be most helpful to the committee if I discuss the request in relation to each of the three organizational components.

I will first discuss the request for the National Institute of General Medical Sciences.

THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Before reviewing the programs and plans of the National Institute of General Medical Sciences, I should like to point out that this Institute has just completed its first year of operations as one of the nine Institutes which now comprise NIH.

In elevating the former Division of General Medical Sciences to Institute status, Congress has underscored the critical importance of support for fundamental research in areas of important relevance to the life sciences.

The Institute of General Medical Sciences administers the NIH grant programs for research in the sciences basic to medicine and biology with particular emphasis on those areas which are common to the needs of multiple Institutes; it also covers certain clinical sciences and multicategorical research not provided for by other institutes or divisions. The Institute also administers the grant programs for training investigators in these fields.

At the present time about 2,000 research projects primarily in basic disciplines such as biochemistry, pharmacology, genetics, physiology, anatomy, pathology, and mcirobiology are supported by this Institute. The individual studies which comprise this activity do not usually relate to any specific disease. They are directed rather to seeking fundamental understanding of structure and organization of biological systems and, increasingly, of those life functions which must be studied at the molecular and submolecular level. In the aggregate, however, they are essential component parts of the categorical programs aimed at the practical problem of solving several medical problems but which having direct relevance to more than a single category of disease can be conveniently grouped within this general activity for administration purposes.

Progress

In a year which saw impressive progress in the general medical sciences, several grant-supported projects stand out as especially noteworthy. I should like to comment first on the work of Nobelist Albert Szent-Györgyi. Last year we advised the committee that this distinguished investigator and his associates at the Marine Biological Laboratory, Woods Hole, Mass., had found in the thymus gland two natural substances: a growth promoter which they named promine, and a growth retarder which they named retine.

Retine has now been found in varying amounts in different tissues, in addition to the thymus, and can be extracted from the urine of children and young adults. Thus, the way has been opened for its large-scale preparation and for more extensive testing of its properties.

The findings of these investigators have led them to consider that the presence of retine, which appeared in proportionately higher amounts in muscle, aorta, and tendon, might explain why cancer rarely appears in these tissues. An age-associated change in concentrations of retine and promine could also account for the more frequence occurrence of cancer in older individuals.

The presence of retine can be identified by its biological action on mouse cancers. Certain malignancies, such as Krebs 2 ascites tumors, spontaneous mammary tumors of C3H mice, and transplanted 180 sarcomas stop growing when retine in small doses is given to mice by injection. Larger doses cause the tumors to shrink. No toxic or undesirable side effects have been observed when either concentrated retine or promine has been injected into mice, probably because both are natural components of tissues.

The retine-promine studies of Szent-Györgyi are intriguing in the context of the total research career of this distinguished scientist, who in 1937 won a Nobel Prize for his discoveries in connection with bilogical combustion processes. In the ensuing years, first in his native Hungary and then in this his adopted land, Albert Azent-Györgyi has followed his educated curiosity into problems in histology, molecular biology, respiration chemistry, muscle chemistry, and other highly basic areas. His current studies, which had their genesis in his interest in an obscure gland, the thymus, give promise of adding new understanding to aging phenomena and associated disease processes. These studies provide an excellent illustration of how basic research, carried on by competent scientists, can lead to unanticipated findings warranting further exploration because of their direct practical implications.

The synthesis of nature's most common organic building block, benzene, is the culmination of 3 years of work for Dr. Eugene van Tamelen of Stanford University and Dr. Socrates Pappas, now at Brandeis University. This is an accomplishment which chemists had believed would never be achieved. Not only have the investigators created the new "Dewar benzene," (named for the eminent 19th century chemist, Sir James Dewar) they also have been able to store the new chemical for months under subzero refrigeration and have even kept it for days at room temperature.

The new molecule contains higher energy, is less stable and so combines more easily with other molecules than natural benzene. The slightly altered ring structure which is responsible for these differences will undoubtedly affect compounds formed with the new benzene. For example, both medicines and plastics incorporating the Dewar benzene will be different from any which have been created heretofore.

Dr. van Tamelen, whose work is supported by a grant from the National Institute of General Medical Sciences, is now studying the molecule itself and the reactions of this unique chemical substance.

So far, only a fraction of a gram of Dewar benzene has been made, but the investigators state that it would not be difficult to synthesize in larger quantities. They themselves have found two ways to make it and believe that there are undoubtedly other ways in which it can be prepared.

The full significance of this accomplishment cannot be immediately evaluated, but it is obvious that the synthesis of this extremely common chemical opens new research potentials of tremendous import.

Another grant-supported study, with broad pertinence to the problem of anemia, was reported by scientists at the Child Research Council in Denver and the University of Colorado. The findings of Dr. V. A. Beal and associates raise questions about the value of iron supplements in children's diet and suggest that more iron than the body needs may cause harm in later years. Normal iron requirements of healthy children proved extremely variable.

Based on their studies, the investigators conclude that children are often fed extra iron unnecessarily and they warn against casual use of these supplements. This research points up the need for better understanding of dietary iron requirements, iron absorption, and iron metabolism as means to combat anemias rather than the indiscriminate use of supplementary iron, with its potential for liver damage in later years.

Within the last decade much has been learned about the processes of exchange of hereditary material in bacteria, a matter of intense interest to geneticists seeking information on evolutionary processes at all levels. Dr. Joshua Lederberg, whose contributions in this field won him a Nobel Prize in 1958, continues, with grant support from this Institute, to uncover new facts about hybridization occurring in different species of intestinal bacteria. Working at Stanford with Dr. P. H. Mäkelä, now at the University of Helsinki, Finland, Dr. Lederberg has succeeded in producing 23 different hybrids of the common bacterium, Escherichia coli, crossed with several species of Salmonella and other intestinal bacteria.

After the investigators succeeded in transferring the *Escherichia coli* fertility factor (an essential of hybridization) to the Salmonella and other bacteria, they found that it became possible for species within these genera to carry on sexual recombination among themselves. A number of crosses of bacterial species indicate that traits are inherited and transmittee to progeny much as they are in higher life forms.

In addition to its genetic importance, this work is of value in studies of metabolic processes and disease causation in general. Hybrids occurring in nature may help explain, for example, why normally harmless bacteria sometimes become highly lethal, as well as the reverse: disease-causing organisms which occasionally become less virulent.

Pharmacology-toxicology centers

To mount a rational attack on some of the new and emerging problems arising from present-day usage in our country of a multitude of potent drugs and chemical weapons, of recent origin, the National Institute of General Medical Sciences is designing a change in emphasis and some expansion of its programs in pharmacology and toxicology.

To make clear the objectives of these programs, several broad problems of growing magnitude and importance can be cited.

Very long-term administration of drugs has become a commonplace of modern medicine practice. More detailed knowledge of side effects is needed to assist the prescribing physician in balancing possible complications against potential benefit, particularly in those instances when anticipated benefit is delayed or expected to be relatively slight.

Experience and observation alone cannot substitute for basic scientific knowledge in the evaluation of safety of new drugs. In addition to empirical testing over periods of long-continued exposure, precise knowledge of the fate and distribution of drugs within the body and the mode of action of active principles is needed for a confident prediction of the effects of long-term chronic exposure. Such knowledge can only come from meticulous studies designed and carried out by scientists who have received the most rigorous training.

In addition to the problems resulting from the increasing use of drugs, there has been a proliferation of new chemical compounds and new uses of old compounds resulting in widespread environmental contamination. Such compounds, including but not limited to pesticides, pose largely unevaluated threats to persons repeatedly exposed, usually to very small amounts, in the course of manufacture or use. NIH regards the pesticide problem as so complex that our research and research training programs in toxicology and pharmacology have been reassessed. It is quite clear that new ways of studying the action of these substances over prolonged periods of time must be undertaken on a scale heretofore not provided for.

Such research and research training will be directed toward providing a general toxicological base for the problems of drug development, the toxicology of pesticides, and the broader problems of protecting human health in a complex chemical world. This will require capabilities and resources beyond those traditionally provided in medical school basic science departments or the talents of any single disciplinary area. We envision a common program development embodying the capabilities in animal physiology of schools of veterinary medicine, the comprehension of ecological systems found in schools of agriculture, the basic capabilities in cell biology of university graduate schools, as well as the traditional disciplines of pharmacology and toxicology.

The development of such a program of research and research training requires the identification of universities with excellence in a variety of sciences commonly found in medical, veterinary, pharmacy, and agricultural schools. Such sciences must be provided with cohesive framework for program responsibility within the university or within two or more institutions reasonably closely situated geographically.

An essential of the program would be the commitment of long-term support to any framework established for the conduct of this research and research training.

The excellence which is an urgent imperative of the program can be best achieved by building slowly and with great care. Within 2 to 3 years, there may be five such centers in operation. A realistic projection for the near future is that two centers might be financed in the first year. This would not include needed new construction, which would have to be financed through the health research facilities program.

Fellowships

To augment the Institute's plans for research and training centers in pharmacology-toxicology, an increase will be proposed in the future special fellowhsip support for training in these fields. This is one of the mechanisms by which the program will be set in motion. Until individuals begin to complete the newly devised training sequence, which at best will become operative only after a deliberately paced beginning in the next year or two, the special fellowships program will be a primary means to broaden the interests and strengthen the capabilities of current staff of institutions chosen to participate in the pharmacology-toxicology program.

Concomitantly, the Institute of General Medical Sciences will continue to support pre- and post-doctoral fellows and research career awardees in the other basic biomedical and health-related sciences for which this Institute is a major source of support.

Medical scientist training program

In another area of training, a development of promise is the recent establishment by the Institute of the medical scientist training program. This program will offer assistance to graduate and medical schools in developing an educational experience which will provide an increasing number of individuals well versed in the medical sciences with a full appreciation of its problems but at the same time broadly and fundamentally trained for a career in science rather than one in the practice of medicine.

The complexities of modern research call for the best training and most efficient use of intelligence that can possibly be devised. The course work now offered for the Ph. D. and for the M.D. degrees each has its own character, one basically quite different from the other. A well-conceived combination essential elements of each degree program would provide training to produce, sooner than is now possible, a scientist well equipped for the conduct of both fundamental and applied biomedical research. This is the scientist so urgently sought today.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

The Division of Research Facilities and Resources (DRFR) provides a focal point within the National Institutes of Health for scientific evaluation, review, and administration of grants which provide facilities and resources to advance the health-related research activities of individual institutions or groupings of institutions.

The programmatic responsibility of DRFR is concentrated in five branches, four of which will be discussed here. The Health Research Facilities matching program for construction of health-related research facilities will be discussed more fully in another context. The three programs requesting a budget of $44,838,000 (including direct operations) are the General Clinical Research Centers Branch, which administers a nationwide program of support for clinical research, the Animal Resources Branch which has one national and six regional primate centers as a major program responsibility, and the Special Research Resources Branch providing computer, biomedical engineering, enzyme, and other large-scale research resources. Each program is designed to offer major support for the health-related activities of institutions by providing physical resources, technical assistance, and professional advice to investigators in all biomedical areas. Each resource is specifically designed to strengthen the research environment of an institution in a planned and systematic fashion and to make available to all biomedical science investigators the highly specialized skills of the resource personnel, together with the complex equipment (that cannot be justified in a single research program or project) which they may require for the furtherance of their own research.

GENERAL CLINICAL CENTERS

General clinical research centers provide a nucleus of skilled physicians, highly trained staff, physical facilities, and special laboratories to advance the field of medicine by providing a bridge between clinical practice and those basic scientific studies which offer new approaches to the treatment of disease. Of 73 centers currently approved, 56 now in operation throughout the Nation provide bedside laboratories where the physician-scientist can develop better methods of prevention, diagnosis, and treatment. Each unit provides a discrete arrangement of laboratories, beds, staff, and equipment designed to permit intensive control of patient regimen under carefully planned and documented research conditions.

Patients are admitted to the units only on the basis of a clinical condition which satisfies an approved research protocol.

The centers now supported vary widely in size and type of operation. There are research centers for adults and for children, for studies of acute burns, sepsis, and trauma, and for studies of premature infants. They range in size from 6 to 30 beds and have from 1 to 7 core laboratories to provide the precise chemical and physical analyses necessary for diagnosis and careful followup of treatment methods. Each center has its own highly trained and specialized nursing staff. In fact, comments from program directors have indicated that one of the most important byproducts of such intensive clinical research in a discrete unit, is the training of nurses who become skilled in the handling of research patients and in collecting research data.

Progress reports from the centers in operation indicate a remarkable stimulus to medical science throughout the country. In addition to the expected increased efficiency and enhanced effectiveness of clinical research, the centers have provided a source for research training of interns and residents, for the training of nurses and dietitians, and for a common meeting place between the clinician and the basic scientist. A constant theme in these reports has been the extent to which these centers serve to upgrade the quality of medical research and patient care.

The marked increase in the quantity and quality of scientific publications in clinical medicine from institutions having general clinical research centers indicates the extent to which these units have influenced the directions of research. Many institutions have reported that the number of clinical investigations has more than doubled. Attacks have been launched upon disease entities not previously under intensive study.

Major accomplishments have been recorded in numerous publications of scientific articles testifying to the excellence of the research conducted in the clinical centers. The use of the artificial kidney to replace the damaged organ in the terminal nephrotic patient has been developed in one center to a point where such patients are now kept alive for long periods of time. Another center is engaged in the delicate and complicated process of transplanting kidneys from donors which include experimentally the great apes, into nephrotic patients. Some patients have now survived for more than several weeks. The lifesaving potential of this procedure is enormous. Still another center has recently developed a machine which will restore normal rhythms to damaged hearts. Before the development of this instrument, the drug, digitalis, was often used, with unpredictable results. Investigators in a general clinical center have tested and enthusiastically reported good results with a drug which is claimed to decrease blood cholesterol, the substance in the body related by some workers to a high incidence of heart and artery disease. A urinary test has been developed which measures the excretion of an estrogen, estriol, in pregnant mothers, and is an indirect reflection of the viability—the capacity for life and growth—of the fetus. A new X-ray technique has been developed by surgeons working at another clinical center, which will better visualize the blood vessels of the brain and provide a more efficient screening mechanism for determining which stroke victims can be most successfully treated by surgery. Researchers in another center developed a test for a urinary constituent which will allow early diagnosis of bladder cancer and thus permit a higher rate of cure.

Funds appropriated in 1964, together with those of previous years, have permitted an expansion in the number of centers and research beds. In 1960 the first 8 centers were approved and today, 73 centers in 30 States have been approved, calling for an ultimate total of 914 research beds. Because of the time required to renovate and staff a facility, only 56 of these centers are actually admitting patients.

The request for 1965 totals $27,684,000, an increase of $539,000. This sum will permit continuation of the centers now in existence, allow for a controlled expansion of the best existing units, and allow for funding five additional centers.

PRIMATE CENTERS

The animal resources program of the Division was established to plan and implement a national program aimed at providing special genetic strains or unusual kinds of well-conditioned animals, much needed in many highly specialized areas of research. The present nucleus of this national effort is the primate research centers program.

In the investigation of diseases of man, scientists can no longer confine their investigations to lower animals. Nor is it ethical in our society to conduct drastic or perilous experiments directly on man. The biomedical research link between lower animals and man is the primate whose physical structure, brain, and emotional responses are most similar to humans.

Detailed observation of rhesus monkeys, for example, makes possible the study of many vital body functions related to problems of human development, disease, and degeneration. A chimpanzee "manned" an important orbital space flight that provided experts in space medicine with vital information regarding body responses to a new environment before risking the life of a human astronaut. Several more are being trained now for the next major step in man's exploration of space. The use of primates in research on tuberculosis, poliomyelitis, cardiovascular disease, and neurophysiology, has produced discoveries of inestimable value to medical practice. More recently, the spectacular transplantation of chimpanzee and baboon kidneys to humans in the terminal stage of kidney disease has pointed up the crucial need for more vital information about primates and their potential value as a source of organs for experimental transplantation to man.

The program now involves six regional centers using the primate as the primary research tool and one national center committed to research with the primate as a research objective. Initial awards have been made for all seven centers. Each award provides two grants: one for total construction costs, and one for annual operating costs. Since the regional primate research centers program began, a total of $14,080,510 has been awarded for construction of the centers. The operating award is made each year following a detailed review of the proposed budget by the Division staff. In every instance, a university is the host institution for the primate research center and, according to the terms of the grants, provides an academic environment of high standard for the center staff and visiting scientists.

Each center has its own program orientation. The National Primate Conditioning Center, located on the campus of the University of California at Davis, is committed to investigations on the primate itself, including the capture and transportation of wild animals, maintenance under laboratory conditions, and breeding and rearing of primates in captivity. The Oregon Regional Primate Research Center features studies in reproductive physiology, cardiovascular physiology, neurophysiology, and work on the origin, specialization and functional mechanism of primate cellular and organ systems. The Wisconsin Regional Primate Research Center specializes in studies on the biochemical factors associated with mental retardation, postnatal development of the brain, hormonal factors in reproductive processes and factors involved in normal and abnormal behavior. The Yerkes Regional Primate Research Center at Emory University is using the great apes, the gorilla, orangutan, chimpanzee and gibbon, in a wide variety of biomedical research studies. The Washington Regional Primate Research Center emphasizes the training of visiting scientists in special research techniques dependent on primates and primate care, and serves as a center for disseminating new data and information about primate research. Emphasis at the Delta Regional Primate Research Center, at Tulane University, is on cardiovascular disease, including experimental, dietary-induced atherosclerosis and hypertension in primates, metabolic diseases, infectious diseases, environmental behavioral studies. The New England Regional Primate Research Center at Harvard University pursues investigations in bacteriology, physiology, nutrition, endocrinology, pathology, psychology, and behavior in primates.

Of the seven centers, only the Oregon center has completed its construction program. Facilities for the other six are in various stages of planning or construction, with research programs now being conducted by all staffs working in temporary quarters.

The increase of $1,300,000 requested for the primate centers program in 1965 is needed to provide major items of biomedical research equipment in newly completed centers and to allow for research expansion and new technical personnel required to make maximum use of the larger and more adequate facilities now coming into operation.

In addition to the need for primates for biomedical research in this country there is an increasing demand for healthy animals of many species of specific genetic background. DRFR now administers four such experimental programs providing animals for research largely supported by NIH categorical institutes.

SPECIAL RESEARCH RESOURCES

The special research resources program of DRFR has as its primary responsibility the support of centralized, large-scale facilities which make available complex and costly equipment and professional or technical skills for the purpose of aiding biomedical scientists in their research investigations. Resources are designed to serve the many and diverse research needs of investigators in various fields of science throughout an entire institution or region. Particular emphasis has been placed on bringing to the biomedical scientist the powerful tools, apparatus, and techniques of mathematics and the physical sciences.

It is not only less expensive to provide a centralized facility to accommodate the needs of many investigators for costly, large-scale, sophisticated equipment which would be used infrequently by any one individual, but is more effective and efficient in promoting new research programs and in aiding existing ones. Within each resource there also exists a competent professional and supporting technical staff which is able to bring its specialized experience and skills to bear upon the particular problems of investigators who are less well trained and sophisticated in these areas.

Twenty-two computer resources, one biomedical engineering resource, one regional biomedical computer technology development resource, and one regional enzyme center are now receiving support from this program.

The accomplishments of this new program have been heartening.

An extensive program was established for the continued development, refinement, and evaluation of a new, versatile laboratory-oriented computer which is designed especially for use by the biomedical investigator. This LINC computer is relatively inexpensive, portable, and will accept a variety of input signals to process data and control experimental parameters during the actual course of an experiment. At the present time 12 of these machines are being evaluated under practical laboratory conditions. Some of the research areas in which the usefulness of the LINC has been demonstrated include neurophysiology, conditioned response studies, physiological control system theory, and mathematical analysis of biochemical and biophysical systems.

Information obtained from the use of these several machines by the investigators will be used to modify and refine the design so that highly flexible and powerful laboratory equipment can be made available to the medical research scientist.

The 22 special research resources in computation and data processing which have been established and supported throughout the country in a variety of medical research environments, have reported many accomplishments during the past year in terms of aid to specific research projects and overall improvement in the environment of the parent institution. Research projects in practically every phase of biomedicine have received support through the provision of machine time and skilled assistance by senior biostatisticians and programers. Projects in blood circulation and coronary blood flow are now being designed to measure the factors which influence circulation, and with a computer to arrive at a mathematical description of the circulatory process.

Intensive investigation of many diseases affecting large populations, including circulatory and coronary artery diseases, requires the computation of vast quantities of data. Such studies cannot be carried out within the usual confines of time and equipment at the disposal of an individual investigator or a small research team. The special research computer resource makes possible the successful prosecution of complex experiments and the simultaneous investigation of a number of variables.

A special research resource in biomedical engineering at Northwestern University has stimulated and made possible a setting in which new techniques and instrumentation have been developed and applied in the areas of sensory physiology, respiratory physiology, cardiology, vascular studies, telemetering of physiological functions, study of mathematical models of body processes, development of transducers for physiological monitoring, electrical anesthesiology and computer applications of various kinds in biomathematics. The resource has provided assistance to a wide variety of projects of interest to the NIH, including the development of an instrument to measure Parkinson's tremor for brain surgery followup; an analog-digital cardiac output meter which measures flow directly and gives written results in seconds; a method for using ultrasonics for the visualization of soft tissues (in preference to X-rays which have detrimental effects); an instrument which provides for an immediate diagnosis of heart disease in schoolchildren; and a method of analog computation to study respiratory defects. One of the scientists in this center has written a definitive textbook in control theory as applied to human living systems.

A contract has been entered into with Tufts University School of Medicine for the establishment and operation of a New England Enzyme Center for the production of expensive, rare, and commercially unobtainable enzyme and biopolymer materials. Four leading New England biomedical research institutions are participating. A national scientific advisory committee has been established and initial studies are underway. In making these needed research materials available, this resource will aid investigators by allowing them to devote their time and efforts to more creative aspects of the substantive research problems in which they are engaged.

As a result of the stimulation of research in those institutions in which special research resources already have been established, the requested increase of $2,515,000 over the 1964 appropriation will be used for continued support of resources established in previous years. In every instance, available funds will be used solely for providing broad-scale support for the diversified research needs of investigators in all areas of the biomedical sciences.

GENERAL RESEARCH SUPPORT

In 1962, the National Institutes of Health inaugurated a new type of flexible award, the general research support grant, for improving health research and research training. General research support grants are complementary to all other forms of Public Health Service grants-in-aid and are awarded to qualified institutions according to a formula based on their previous health research expenditures. This formula provides incentives to increase the institution's commitment to health research without displacing funds already available for that purpose. Although full details on use of the awards are available for only the first year of the program, it is already clear that the purposes for which the general research support program was established are being met.

General research support funds provide institutions with an increased measure of freedom and responsibility for allocating a part of the Federal funds locally available for the support of health-related research. This permits institutions an increased measure of control over the quality, emphasis, and direction of their own research activities: institutions are enabled quickly to redress program imbalances without restriction as to specific scientific problems, discipline, and disease entities; funds can be utilized flexibly, so as to meet different needs year by year, and catalytically, so that other forms of support, non-Federal as well as Federal, are engaged promptly and efficiently, as soon as any given research activity reaches maturity. General research support permits institution to reap maximum advantages through local insight into the best means to identify and support research excellence among emergent research ideas and techniques provided by the faculty and staff.

In 1962, priority was given to schools of medicine, dentistry, public health, and osteopathy, institutions which train individuals engaged in direct health care. Awards totaling $20 million were provided to 153 such institutions. Over 82 percent of the total went to medical schools, 10 percent to dental schools, and the remainder to schools of public health and osteopathy. Institutional needs for salaries and permanent equipment accounted for two-thirds of the total disbursements. Over 1,200 professional research personnel, 800 technicians and research assistants received support for their direct research contributions; over 2,000 trainees and research fellows improved their skills for the conduct of research.

According to the institutions' annual progress reports, general research support advanced institutional and individual research planning and research program development; supported new areas of research without delay; enabled recruitment of professional staff who introduced new skills and ideas to the institution and attracted additional research personnel and funds; encouraged more flexible interdepartmental and interdisciplinary collaboration in research; bolstered trainee recruitment, retention, and qualification; enabled institutions to improve the quality and vigor of research in backward as well as new departments; provided central research resources, thus broadening the base of future research activities; and primed the pump for attracting outside support for research. In this last regard, more than $5 million were attracted from private sources to grantee institutions during the first year of the program alone, as a direct result of use of the general research support grant. This represents about a 25-percent dividend on the original $20 million provided through this program.

The general research support program was funded at $20 million in 1962, $30 million in 1963, and $35 million in 1964. In 1963, the program was extended to include 13 additional health professional schools and 98 other research institutions such as hospitals, research organizations, and State, city, and county health agencies heavily engaged in health related research. In 1964, an additional 37 institutions are expected to enter the program. For 1965, a budget of $40 million is projected.

OFFICE OF INTERNATIONAL RESEARCH

Introduction

The Office of International Research provides a focal point within NIH for policy formulation and guidance and coordination for all NIH international activities. These activities have been established in response to the objectives outlined by the Congress under the International Health Research Act of 1960 (Public Law 86–610). The law seeks to "advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research and research training."

The research itself has, however, a more compelling and more practical purpose. The basic reason for supporting research outside the United States is the variety of unusual or unique opportunities existing in foreign countries to pursue studies of substantial importance to medical science and to the health of Americans. Investigations on an international basis in the fields of geographic pathology and epidemiology contribute important clues to the causes of certain disease which cannot otherwise be studied adequately.

For example, the incidence of both atherosclerosis and cancer may well be affected by heredity as well as environment, and the effects of these factors as well as their separation can often be studied only in foreign countries. The fact that susceptibility to coronary artery disease is, in part, related to diet was to a major degree suggested by studies overseas in populations with diets substantially different from those of Americans. In the fields of infectious disease, nutrition, and genetics, many important discoveries of direct relevance to the health of the American people have been made by exploiting research opportunities in other countries.

General policies and budgetary levels

After a period of growth, support of research in other countries by NIH through the research grant mechanism will decrease in fiscal year 1965 for the first time. Total PHS foreign research grant support will be $13.5 million in 1965 as compared with $15 million in 1964. There will be a decrease from $8.5 million to $7 million in research grant expenditures in Canada, Western Europe, Australia, and New Zealand. This decrease is in response to the need expressed by the administration to reduce dollar expenditures in countries where such expenditures aggravate the gold drain problem. Every effort will be made by the OIR, working with the Institutes and foreign governments, to plan activities with other countries, if they so desire, to insure that the reduction in U.S. support will result in more extensive sharing of the costs of research rather than an interruption of research in progress. It should be emphasized that this research is not being reduced because it lacks domestic purpose and satisfied domestic need.

Programs.—(*a*) The Office is also directly responsible for the administration of a number of programs, among which are the international centers for medical research and training, international postdoctoral fellowships, the international research career development program, and the special foreign currency program. In addition, this Office administers the NIH oversea offices which develop and gather information related to our foreign activities. The estimates for these programs, with the exception of the special foreign currency program, are contained in this appropriation. (*b*) Oversea offices: The NIH offices overseas were established in 1961 to carry out the following responsibilities:

(1) Acquisition and collection of information on the biomedical sciences. This involves visits to laboratories and other institutions to observe the manpower, facilities, techniques, and other resources involved. Firsthand discussions are held with the staffs of the laboratories. This information is then collated and evaluated before transmission to NIH for dissemination.

(2) Continuing critical appraisal of the productivity and of the secondary effects of NIH foreign activities. This requires periodic visits to institutions carrying out research or research training under NIH grants. In addition, the offices evaluate scientific trends and changes in the policies, practices, priorities, and goals of foreign science.

(3) Representing the National Institutes of Health with regard to its foreign extramural programs. Maximum effectiveness of these programs requires on the scene contacts and consultations with foreign scientists, foreign science administrators, and foreign and U.S. Government officials working abroad.

(4) Upon request of the Institutes, the Division of Research Grants, and whenever feasible, other elements of the USPHS, these offices carry out spe-

cific functions such as project site visits on proposed grants or contracts, negotiation of Public Law 480 research agreements with foreign governments, etc.

Effective operation of these offices is critically important to effective administration of NIH programs. For this reason, the staffs of the offices are carefully chosen scientific personnel with cultural, academic, and professional backgrounds which make them particularly suited to the assignment in a particular area.

Training activities (international research career development program)

The Public Health Service has been involved with health protection measures, such as foreign quarantine, in other countries for decades. With the development of medical research not only in this country but throughout the world, it is clear that the Public Health Service involvement with medical research conducted in other countries will be continuing. Yet the Service has few people who have been specifically trained to conduct and administer research outside the United States. To meet this need, the National Institutes of Health international research career development program is providing opportunities for promising young scientists to work abroad as members of established research groups. This has been done by providing for assignment of 8 to 10 Public Health Service commissioned officers each year to research projects and programs overseas. International research career development associates are assigned to selected research units and trained by senior preceptors while performing needed professional services. For example, at the SEATO Cholera Laboratory in Pakistan scientists of the National Heart Institute are exploiting a unique opportunity for studying water and electrolyte depletion and repletion phenomena. Investigators in the National Institute of Arthritis and Metabolic Diseases are studying the epidemiology of diabetes in connection with nutrition surveys in foreign countries.

Grants—research (International centers for medical research and training)

International centers for medical research and training (ICMRT) represent a cooperative endeavor, supported by NIH research grant awards to U.S. universities, in which research and training centers have been developed at domestic and foreign affiliate sites to conduct medical investigations relevant to U.S. domestic research interests. A distinguished Advisory Committee on International Centers was established to provide advice on applications for grants to support centers. The development of a series of five international centers with the advice of the Committee, has created unusual opportunities for American physicians and scientists to pursue productive research careers in a foreign setting. A corollary is the stimulus the ICMRT program has provided to scientific personnel within the collaborating foreign affiliates to develop additional medical research and training resources in the participating host countries.

Each international center currently in operation consists of two basic operational elements: (1) A university-based organization devoted to a research and research training program in the U.S. which is closely related to the specific research and training activities conducted within (2) an overseas counterpart facility where American scientists may take advantage of unusual or unique environmental, ethnic, and medical conditions not available for study within the continental United States.

The five sets of cooperating institutions are as follows:

U.S. university	*Foreign cooperating institution*
Johns Hopkins University	All-India Institute of Hygiene and Calcutta School of Tropical Medicine, Calcutta, India.
University of California	Institute of Medical Research Kuala Lumpur, Federation of Malaysia.
Tulane University	Universidad del Valle, Cali, Colombia.
Louisiana State University	University of Costa Rica, San Jose.
University of Maryland	Institute of Hygiene and Lahore General Hospital, Lahore, West Pakistan.

The initial phase of the program devoted to the administratively complex task of developing foreign research facilities in collaboration with selected foreign universities and research institutions has been completed in each of the centers. All centers are now actively engaged in specific research projects.

A substantial portion of current research is focused upon the demography, epidemiology, and ecology of disease states of concern to the United States and the host nation. A multidisciplinary approach is being developed within the several centers to study more effectively the complex biomedical problems which prevail at the foreign sites. As a consequence, professional staffs are being developed and trained to investigate, through a selective amalgamation of basic science, clinical and public health research methods, not only tropical diseases, but a wide variety of other disease states which exist in these countries. Accordingly, the scientific programs in each center will progressively encompass the full spectrum of factors which directly or indirectly influence disease in the United States and abroad. These programs include studies of social and other environmental factors which may be related to the development and persistence of acute and chronic diseases. The presence of distinct ethnic and demographic groups in foreign areas permit studies in depth of physical and biomedical factors which may be involved in racial susceptibility to disease.

In addition to the research in progress and being planned, each university is creating an effective training program for U.S. citizens at both the domestic and the oversea sites. Each center has been unusually successful in attracting well-trained young physicians and scientists who wish to further their experience and careers in international medical research.

Research and technological accomplishments now emerging from the international centers indicate that the program is not only contributing substantially to fundamental knowledge and to our pool of urgently needed U.S. scientific manpower, but is effectively promoting the development of indigenous biomedical resources of high priority to the host nation. This request will continue this program at its present level.

Grants—Fellowships, international postdoctoral

International postdoctoral fellowships are awarded in order to make available to medical science in the United States the most capable younger investigators in the world. In addition, the fellowships further strengthen the research capacity of the fellows and of their native countries.

Since 1958, international postdoctoral fellowships have been awarded to promising foreign scientists for training in biomedical research. In fiscal year 1964, 100 fellowships were awarded, bringing the total to about 400. In fiscal year 1965 about 115 fellowships will be awarded. This program has enriched American research, and has also built research capabilities in other countries. It enables foreign investigators to share their ideas, background, and insights, with American investigators. Training in laboratories in the United States typically has the effect of stimulating a long-term interest on the part of a foreign investigator in health problems of concern to the American people. This interest is almost invariably carried back to his own country where research on the same or related problems is continued. Experience has demonstrated that the international fellowships have enhanced collaborative research and have helped to strengthen research environments to which American scientists have gone for specialized research. In short, this investment in emerging world leaders in medical research is a highly productive one for the United States. This request will continue this program at its present level.

In conclusion, Mr. Chairman, the recommendation for "General research and services" for 1965 is $163,745,000 compared with an operating level of $153,210,000 for 1964. The attached table shows the activity distribution as related to the administering organizations.

GENERAL RESEARCH AND SERVICES, 1965 APPROPRIATION REQUEST

Activity distribution related to administering organizations

	National Institute of General Medical Sciences	Division of Research Facilities and Resources	Office of International Research
Grants:			
Research:			
Regular projects grants	$53,246,000		
Scientific evaluation grants	1,200,000		
General research support grants	4,841,000		
Primate centers		$7,000,000	
Special resource centers		8,200,000	
General clinical research centers		27,684,000	
International centers for medical research and training			$3,000,000
Research fellowships	13,765,000		1,200,000
Training grants	37,182,000		
Direct operations:			
International research			1,147,000
Training activities			165,000
Review and approval	1,599,000	1,230,000	
Program direction	562,000	409,000	
Collaborative studies	1,000,000	315,000	
Total appropriation	113,395,000	44,838,000	5,512,000

SUMMARY OF BUDGET

Dr. SHANNON. This appropriation provides support for the general, noncategorical operating programs of the National Institutes of Health. The 1965 request totals $163,745,000 compared to the 1964 operating level of $153,210,000, or an increase of $10,535,000.

The programs covered are those of the National Institute of General Medical Sciences (formerly the Division of General Medical Sciences), the Division of Research Facilities and Resources, and the Office of International Research which, until last year, was represented as a part of my immediate office.

The National Institute of General Medical Sciences supports a broad program of research in the natural and behavioral sciences and in some clinical sciences, all of it essentially noncategorical in nature but relevant to the research of the categorical institutes. Graduate training programs in research, and research fellowships are also supported by this Institute. The total appropriation request for its activities is $113,395,000. Dr. Powell is here to defend this in detail, according to your wishes.

The Division of Research Facilities and Resources, in addition to administering the health research facilities program for which there is a separate appropriation, provides facilities and resources to meet the broad health-related research needs of institutions and groups of institutions. Among these are general clinical research centers, regional primate centers, and special resource centers for computer operations and in biomedical engineering. The request for the programs of this Division is $44,838,000. Dr. Stone is here to discuss the details of this activity.

The Office of International Research, besides providing a focal point within NIH for policy formulation and guidance and coordination for all NIH international activities, administers the international centers for medical research and training, international postdoctoral fellowships, the international research associate program, and the special foreign currency program. The latter is presented in a separate appropriation, and Dr. Kidd is here to cover the details of this activity at your pleasure. The request for the Office of International Research is for $5,512,000.

I suggest, Mr. Fogarty, that the best entrance into this rather complex appropriation is with the National Institute of General Medical Sciences in the budget justification. This starts on page 2 of the congressional submission.

APPROPRIATION STRUCTURE

Mr. FOGARTY. We had a little discussion last year about the desirability of having the appropriation structure on the same basis as your organization. You do have three distinct divisions under this one appropriation, do you not?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. And it seems to me there is no more, in fact there is less relationship between the "Office of International Research," and the "Division of Research Facilities and Resources" than there is between some of the other Institutes that are budgeted for individually. Isn't that right?

Dr. SHANNON. I would agree with that sir; yes, sir.

Mr. FOGARTY. Will you submit appropriate language for the bill in case the committee decides to separate these three?

Dr. SHANNON. This we will be glad to do.

Mr. FOGARTY. Taking reserves and transfers into consideration, these three organizations have $153,210,000 available in 1964 and are requesting $163,745,000 for 1965.

Dr. SHANNON. Yes, sir.

ACTIVITIES TRANSFERRED TO INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. FOGARTY. This year, you are transferring $9,646,000 to the new Institute of Child Health and Human Development. What activities were transferred?

Dr. SHANNON. Dr. Powell.

Dr. POWELL. The activities transferred to the new National Institute of Child Health and Human Development were transferred by mutual agreement between Dr. Aldrich and myself. There were no complete and distinct units of our program which were transferred; rather, we selected those activities in our research grants, those activities in our training programs, and those activities in our fellowship programs, which seemed to be most closely allied to the objectives of the Child Health Institute and its programs in the area of human development previously supported by the Institute of General Medical Sciences.

In addition, the Center for Research in Child Health and the Center for Aging Research were transferred as units.

Mr. FOGARTY. They have not transferred as activities?

Dr. POWELL. They were not transferred en bloc but selectively, as elements which relate more closely to the mission of the Child Health Institute.

UNPROGRAMED FUNDS IN 1964

Mr. FOGARTY. You have unprogramed funds in 1964 totaling $996,000. Is that right?

Dr. SHANNON. That is right.

Mr. FOGARTY. What is the reason for that?

Dr. SHANNON. There is an estimated unobligated balance of $996,000 related to the total "General research and services" appropriation. This was placed in reserve in connection with the estimates made last fall at which time these funds did not appear to be required for research programs.

Mr. FOGARTY. Congress did not make any change in the budget you presented last year, did they?

Dr. POWELL. No, sir. That is right.

CENTERS OF PHARMACOLOGY-TOXICOLOGY RESEARCH

Mr. FOGARTY. To make this a little easier, I will try to group my questions by organizational unit. First, the National Institute of General Medical Sciences.

I notice on page 21 you propose to—

> encourage the development of, and provide support for, centers of pharmacology-toxicology research.

Tell us what you propose here.

Dr. POWELL. We are concerned about the immediate problem of additional research and research training in the fields which underlie the development of drugs and in related fields involving problems stemming from the presence of toxic substances in the environment.

We do not have specific institutions for such research in mind at the moment. This is still under study. However, the plans we are drawing up envision the grouping of research and training programs in institutions which already have available competencies in a medical school, a dental school, a pharmacy school, and, perhaps, in a school of agriculture because of research interests in the pesticide problem. We would provide these groups with the financial support needed to develop more integrated programs of research and training.

Mr. FOGARTY. Is there any agreement that you have with the Food and Drug Administration in this area?

Dr. POWELL. There is an agreement between NIH and the Food and Drug Administration with regard to communication of information. This agency is aware of our program interests in the field. We have plans to develop this as a basic resource for maintaining full and prompt interchange of information. We believe it will meet the needs, at least in part, of their programs as well as ours.

FUNDING THE CENTER

Mr. FOGARTY. You say initial support in 1965 will be about $500,000 each. What do you estimate the annual support would be after 1965?

Dr. POWELL. We visualize that the annual support for the year or two after the first year will drop, perhaps to the level of about $250,000 or $300,000 per year per institution, once they have satisfied the needs for initial funding and major equipment acquisition. Then we would expect that as the training programs and research programs develop, needs would again increase, necessitating financial support at approximately the original level; so we anticipate at this stage an on-going level of support of $500,000 in 3 to 4 years.

Mr. FOGARTY. What percentage of the total cost of these centers would you propose to bear?

Dr. POWELL. This would depend upon individual factors governing each center. We would propose to assume that proportion of the cost that we thought had to be borne in order to make it possible for the centers to accomplish their tasks. Basically, that is the way we would try to apportion costs in our proposal.

Dr. SHANNON. I think—it is my personal guess—that these centers cannot be established short of total funding from a Federal source. The problems of general toxicology are such that they do not fit in with the education and other programs of any of the institutions that have the competencies to carry out what needs to be done. Consequently, we are going to have difficulty. These centers will have to be developed in parallel with the university structure, and will require —in my estimation—total funding.

We have a broad program of training in the more conventional aspects of pharmacology such as are performed and carried out in a medical school. As a result of study which we completed almost a year ago, we became quite certain that departments of pharmacology do not have the view or the attitude of mind that would permit the study of drug or chemical intoxicants, in small quantities, over very long periods of time and with very large groups of factors involved. It is quite conceivable that before these centers are evolved, we may have to arrange them to be run by contract rather than by the grant mechanism.

This type of research is really closer to industrial research than it is to academic research. The study we have undertaken during the past year does not indicate to our minds that there are a substantial number of university environments that are anxious to develop this type of activity. It is going to be very difficult to develop. I think it is going to be very costly. I think the figures that Dr. Powell has given you, $500,000 a year, as the ultimate cost, I would place as a minimum. I think in order to give broad coverage to the development of fundamentally oriented toxicology, both from the standpoint of research and training, you want to look forward to the need of probably three to five such centers in different parts of the country, addressing themselves to quite different aspects of the problem.

Mr. FOGARTY. If it is that fuzzy, why should we develop any centers?

Dr. SHANNON. I think that what we would like to do—do you mean why not do it ourselves?

Mr. FOGARTY. Or not at all.

Dr. SHANNON. I think what we would like to do is involve some of the university oriented talents already available in schools of pharmacology and medical schools; we think that the combined jobs of research and training in such a setting would be better handled in several peripherally located institutions around the country, than if we were to try to do it as a direct operation.

JUSTIFICATION FOR THE CENTERS

Mr. FOGARTY. Tell us why it should be done at all. What is the main reason for it?

Dr. SHANNON. The main reason basically is that during the past 10 or 15 years, as a result of our industrial development, the ordinary citizen is exposed to an intrusion from without of a variety of chemical intoxicants. There are water pollutants, for example, and they are properly taken care of in the water pollution program. There are also air pollutants. But in addition, we are now finding that, in the course of preventing disease, there are also a substantial number of chemicals that are used as drugs, and literally introduced into the system at a relatively early age and contained there for years. The common characteristic of all of these potential intoxicants is that they are given in small doses, that they are quite active chemicals and are given over a very long period of time.

The problem of potential interaction of one drug with another, or the problem of interaction of one chemical substance with another—the model systems that can test in a meaningful way these complex toxicological responses are just not in being. What this requires is the study of a number of animal populations for substantial periods of time, and in many different ways. Cases will involve not only live studies on specific animals, such as mice, hamsters or the like, but studies on succeeding generations, because some of these chemicals have what are called mutogenic properties.

That is, they have the ability to interfere with the transmission of genetic characteristics, with the present reproductive process. I might say that the rather small study that the Cancer Institute has undertaken in association with AEC at Oak Ridge is the only study going on of this general nature in this country. The importance of this type of study and the desperate need for this type of installation has been given recognition, for example, by the World Health Organization; and the Director General proposed such studies when the executive committee met in January. They in fact set up an institute on the shores of Lake Geneva to address themselves specifically to the problem of mutogenesis. We in turn, have proposed to them studies of the type we feel are important to this country. If these cannot be done except in a few quite large countries, this would be a suitable area of research activity for the World Health Organization to foster information activity so that results are made known generally, both to developing and advanced countries. The need is to develop information that will permit the evolution of meaningful models for transfer of experimental data to lines of demand.

At the present time, we do not have those models.

Mr. FOGARTY. Will the building of these centers lessen the necessity of building an environmental health center?

Dr. SHANNON. No, sir.

ENVIRONMENTAL-HEALTH-TOXICOLOGY RELATIONSHIP

Mr. FOGARTY. There is some connection between environmental health and toxicology?

Dr. SHANNON. There is a connection here, in the general field of toxicology, if you will, and I am sure the Department will be quite glad to have you see our staff paper which was presented to the Public

Health Service—or Dr. Terry's office, I should say—about 6 months ago and from his office to the Department, in association with similar plans of the Food and Drug Administration. Everybody addressed themselves to the very pressing problem of the insecticide hazards. We were asked to comment on what programs could be developed that would be meaningful in terms of the specific kinds of insecticides. At that time, we pointed out that the insecticides presented a very special problem in the field of general chemical intoxicants, that we had hoped would be taken care of by the general program—pharmacology, toxicology.

We went on to say we have been examining the elements of that program during the past year very carefully and were convinced that these needs were in fact not being satisfied, and proposed that what we do is to go forward with the setting up of the general toxicological program, in much the manner I described to you.

Mr. FOGARTY. I remember last year, you laid great stress on doing something in the field of toxicology.

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. It seems to me you were more emphatic last year than this.

Dr. SHANNON. If I sound less emphatic this year than last year, I do not mean to.

Mr. FOGARTY. I remember last year, you said it was one of the most important things you had to get going on, and this year, you don't seem to be so emphatic.

JUSTIFICATION OF CENTERS

Let me put the question another way. What will be the consequence if we don't build these centers?

Dr. SHANNON. We expose ourselves to an unknown hazard. I feel no uncertainty that we will return to discuss this problem next year and will be unable to indicate to you that we have made anymore advances during the coming year than we have during the past year because to mount the type of program we have in mind, that we feel is desperately needed, is generally, I believe, beyond the legislative authority we have to work with. I think this is a very good example of a research area that will require construction of a facility at full cost to the Federal Government, and the running of that facility by contract with full cost paid by the Government.

We do not have the authority to do this. I do not feel we will be able to develop within the program plans we have the type of facility that is so desperately needed in this area. This was pointed out to the Public Health Service and to the Department, and in our preliminary 1966 budget we will emphasize the need for legislative authority to undertake this type of program.

Mr. FOGARTY. Why do you not ask for legislation now?

Dr. SHANNON. We have asked for legislation during the past year and it has not been granted.

Mr. FOGARTY? By whom? The Public Health Service or the Department of Health, Education, and Welfare?

Dr. SHANNON. I do not know, sir.

Mr. KELLY. My recollection of it is hazy but I do know, at the time the Department prepared its comments on the "Science Advisory

Report on Pesticides," we recommended that in order that the Department would be better prepared, to perform its responsibilities under that report, or the recommendations of that report, that legislation be specifically sought to permit contracting for the support of toxicological institutes. That was forwarded to the Bureau of the Budget. I cannot recall whether this was converted to a legislative proposal, and the administration forwarded it to Congress or not. I would like to check it and insert the answer in the record.

Dr. SHANNON. I am very hazy. It was not forwarded as a legislative proposal, I am sure. We will have another opportunity to recommend it.

Mr. FOGARTY. Would we be on sound ground to appropriate funds for these two or three centers when you are going to come in with a new legislative program in this area?

Dr. SHANNON. Well, sir, I think that we will try to establish these within the limitations we have. With these funds at this point of time, it will be possible to rent laboratory space and take such action as is necessary to get the program started, but I would point out that this is a step that is likely only to be taken if the legislative authority for a more reasonable program is in the offing.

In the absence of that, I would say that at this time, the unwillingness of this committee to support this type of activity would be indicative of an unwillingness to make any attempt to solve what I believe is a very serious problem at the present time.

ORGANIZATIONAL RELATIONSHIP WITH FOOD AND DRUG ADMINISTRATION

Mr. FOGARTY. In the past year, have you entered into any agreements with the Food and Drug Administration on any program? The Citizens Committee on Food and Drug did make some recommendations.

Dr. SHANNON. Our primary point of contact with the Food and Drug Administration has been Dr. T. J. Kennedy, who has been in extensive contact with them and I would say we have formal exchange. We have formal notification processes, and these are used. These are not simply a matter of form. It may be that Dr. Kennedy might be more specific.

Mr. FOGARTY. Did not the Citizens Committee that looked into the Food and Drug Administration make some specific recommendations along this line?

Dr. SHANNON. The primary recommendation that the Citizens Committee made was that there should be established an—I forget what they called it—a research institute that would specifically address itself to the problems of drug development and of food problems.

Mr. FOGARTY. They did not recommend the NIH?

Dr. SHANNON. No, sir.

Mr. FOGARTY. Did they accept any of these recommendations?

Dr. SHANNON. No, they did not.

Mr. FOGARTY. This recommendation was not acceptable to whom?

Dr. SHANNON. I think the Secretary felt—I don't recall the specifics of it—but the change in organization that he did accept on the advice of the Citizens Committee did not provide for broad strengthening of science in the many branches within the Food and Drug Administration and the setting aside of certain resources that were not related specifically to the control process. But I am not clear in my mind as to the precise extent to which he did or did not follow the Citizens Committee recommendation.

Mr. Fogarty. Well, I do not have the recommendations in front of me now but I was thinking they critized your relationship.

The Food and Drug Administration has been critized by Senate committees. Have any Senate committees made any recommendations to the Institutes of Health about assuming any responsibilities of the Food and Drug Administration?

Dr. Shannon. Yes, sir. On the Senate side, Senator Humphrey has felt that we should take a much more active part—or play a much more active role in some of the areas, where, as he views it, there is gross overlap between the responsibility of the Food and Drug Administration and ourselves, and indeed, there is some overlap. We are concerned with the problems of development of drugs, and the determination of the toxic hazard of new drugs as well as the determination of utility of new drugs.

The Food and Drug Administration, on the other hand, is concerned with these same problems from the standpoint of control. Senator Humphrey has felt that there should be much more detailed report from our operations to the Food and Drug Administration and, in fact, from all Federal operations. By and large, this is being provided for now by the Veterans' Administration; by the Public Health Service hospitals; and by the Department of Defense activities as well as a fairly large group of civilian hospitals across the country. This we are glad to do. But we feel that, in reporting toxic hazards that are studied incidental to the evolution of new therapeutic agents, that the logical reporting point of toxicological happenings that would be useful to the Food and Drug Administration is the hospital unit. When patients are being studied in clinical investigating situations many things are happening to them other than the simple treatment of disease. They receive large numbers of drugs of one sort or another, from such conventional items as aspirins or sleep aids, antibiotics, to quite specific medicinals. These patients, however, represent only a very small part of a substantially larger hospital population group. For a scientist to feel that he must report a toxicological observation through our channels to the Food and Drug Administration is to provide toxicological information without documentation of how often it occurs in relation to a large population group. Consequently, this type of toxicological information is not meaningful.

On the other hand, when one views the total hospital population and a relationship is established, between the hospital administration and the Food and Drug Administration, such that, above a certain threshold of importance, all toxicological phenomena are transmitted to the Food and Drug Administration, then this type of toxicological information becomes meaningful.

So that we have resisted an attempt to try to convert our grant programs into a reporting system on toxicity.

On the other hand, when toxicity comes to our attention, the Food and Drug Administration is immediately notified. I think there have been some other differences of opinion as to the role that NIH plays within the general field of information. This is a very controversial point because it is our feeling that this is an area that may perhaps be, to a large degree, centered within the information services of the National Library of Medicine.

In point of fact, a study has been going on for the past 6 to 9 months within the Office of the Surgeon General, to determine whether the Public Health Service should set up—quite apart from the National Institutes of Health—a drug reporting center.

As an individual, I don't happen to favor this type of organization structure. I think that to pull out information in this manner is to separate it from the program on the one hand, and medical communication on the other. I think the tendency is to become an autonomous entity. It is not perhaps sufficiently responsive to the need. In any case, this is under study at the present time, and it was proposed for discussions with the committee called together by the Federation of American Biological Societies some 2 weeks ago. They in turn were not too terribly impressed by the proposal, but advised that this was a matter that could be more suitably looked into, from the standpoint of reasonableness of the proposal, by the Committee on American Drug Development and Drug Hazards that has recently been created within the National Research Council.

Now, I think that we cannot help but feel that there is a broad function that is not being adequately handled at the present time. People are looking for a way to establish this as a normal function in a proper organizational setting, so that the job that needs to be done gets done. It is not being done now.

I just happen to feel that it would be an intrusion into the primary objectives of the program of NIH for us to attempt to accomplish this need. In this—and we have stated this quite bluntly—I think we have the concurrence from the Office of the Surgeon General. But they in turn are searching for their own solution of how this should be handled. When they reach a decision there, I am sure that this has to be discussed with the Department because, again, the Food and Drug Administration is very intimately concerned with how this is handled conventionally.

Now, it may be that I am not fully informed of the present status but Dr. Price might wish to add something.

Mr. Fogarty. Do you wish to add anything, Dr. Price?

Dr. Price. No. This is essentially where the matter stands. The major issue has been whether this is a function which could best be developed within an organization that deals with informational materials, like the National Library of Medicine, or set up in some independent fashion, and these are the questions that have not yet been resolved.

RESEARCH GRANTS BUDGET

Mr. Fogarty. All right. The major part of the increase, Dr. Powell, is for research grants, an increase of $3,856,000. Practically all of this is to continue going projects. You are actually proposing to cut back by 15 the number of new applications you will be able to fund, is that right?

Dr. Powell. Yes, sir.

Mr. Fogarty. So you are not even keeping pace with 1964? You are going backward.

Has this program been determined expendable by someone?

Dr. Powell. The program has not been termed expendable. We will have essentially, in our present estimate, precisely the same amount for new grants in 1965 as we have in 1964. The average size of our grants at NIH is increasing, so that the actual number will decrease slightly with the same funds.

Mr. Fogarty. But as I understand it, you are cutting back by 15 the number of new applications you will fund.

Dr. Powell. That is right.

Mr. Fogarty. So that is not even holding your own ground. That is going downhill. Tell us some of the new developments in this research on heredity, and instrumentation; pesticides; anesthesiology.

Dr. Powell. Would you let me take one at a time, sir?

Mr. Fogarty. Yes. I meant for you to.

RESEARCH ON HEREDITY

Dr. Powell. The congressional justification contains a discussion of the current status of the research on heredity. The advances during the past year have certainly not been as striking as the advances over the previous year.

There have been continuing developments on the details of the genetic code; the nature of nucleic acids and their influence on cell growth and functions have continued to be studied.

I would not feel we have made, as I said, the advances in the past year that were made previously.

ORGAN TRANSPLANTS

Mr. Fogarty. All right. What about organ transplants?

Dr. Powell. Organ transplantation has been moving forward more rapidly, primarily with the development of chemical methods of interrupting the reaction of the receipient of an organ transplant, thus reducing the likelihood of rejection. This, unfortunately, when done by drugs, is also accompanied by a decrease of resistance of the body to other foreign agents, such as infectious organisms. Nonetheless, I think that many of us feel that there have been significant advances during the past year in the practical field. In addition, at the more fundamental level, there have been significant advances in the field of hypersensitivity. Recent studies suggest, for example, that childhood eczema may stem from an individual's sensitivity to his own skin—an allergic type of reaction. Such studies help extend our understanding of the immunology of organ transplantation—why the body acts to reject foreign tissue and how this immune reaction can be modified and perhaps even overcome. We feel that we are making definite and significant progress. We have made progress in the past year.

Dr. Shannon. One of the other institutes has a major scheduling here because, as Dr. Powell has pointed out, it is the rejection of the organ after circulation is well established that is the main problem now. Surgeons have done their job very well.

Now it becomes possible to transplant livers, kidneys, lungs, and in fact, there even have been transplants of the heart; but the problem of rejection involves the capability of the body of reacting against any foreign protein, as part of a normal and necessary response.

I would point out that I think that this field of organ transplant is receiving much too much attention in the popular press today in relation to the state of our knowledge—and I say that without criticizing the individual scientist who has brought the field up to its present stage. It appears to me that, from here on, this is not a field for exploration of surgical techniques. They are quite adequate at the present time. This field now needs more penetrating insight into the considerations that result in organ rejection, rather than simply the establishment of an organ in the body.

This is not a new phenomenon. It is not generally understood how fantastically successful certain of these transplants are in the case of a small number of identical twins, that have acquired a new kidney; but also, the devastatingly poor results that can occur at the other side of the situation. You see, if you poison the capacity of the body to resist heterologous tissue so it cannot react adversely to the new organ, it will also attenuate the capacity of the body to fend off invading organism so that these people are extraordinarily susceptible to disease. Up to the present time, there has not been found a way of providing for successful supression over extended periods, or successful in a substantial number of cases.

ANESTHESIOLOGY

Mr. FOGARTY. Tell us about anesthesiology?

Dr. POWELL. In the field of anesthesiology there have been major developments in terms of instrumentation for the patient. Our anesthesiology research as been on the basic problems of the absorption, and the transfer of anesthetic agents across the membranes. In addition, our largest single effort has been in the prosecution of a research project aimed at determining whether or not the very commonly used anesthetic agent, halothane, has any toxic effect on the liver as has been suspected.

The project has been going forward under contract with the National Academy of Sciences—National Research Council, with the collaboration of some 30 institutions which are at the moment reviewing their anesthetic records—patient operative records—to determine whether or not there has been an increase in cases of liver damage when one compares the use of halothane with other anesthetic agents. This study has not progressed far enough yet to report any conclusions.

INSTRUMENTATION

Mr. FOGARTY. What about this area of instrumentation?

Dr. POWELL. In the area of instrumentation, there have been instruments developed for such specific purposes as the measurement of wound healing; studies are also going forward, looking toward the development of biological power sources for possible use inside the body, as with artificial pacemakers for the heart. But I believe that the most striking and interesting advances have come in the field of electron microscopy and related areas in which scientists are greatly extending our capacity to visualize structures within cells and within parts of cells. This has been combined more recently with chemical techniques, specific chemical approaches, to make it possible to visualize what the actual composition of materials and parts of a cell may be, even when they are present in very small, very minute quantities.

NATURE OF WORK ON PESTICIDES

Mr. Fogarty. What about pesticides? Tell us how different your work is from the work done under the Enrivonmental Health appropriations.

Dr. Powell. I think some of this, Mr. Chairman, has been alluded to already.

The Institute of General Medical Sciences does not undertake, or does not support activities which are primarily directed toward applied toxicity problems involving pesticides. The determination as to how pesticides contaminate the environment and what the practical problems are rests with the Public Health Service's Environmental Health group.

Our activities, rather, are directed toward the basic toxicity problems—questions relating to the make-up of compounds which are toxic and to the nature of their action on animals and man. I might say that it is sometimes extremely difficult to differentiate and classify an individual project which might extend into both basic and applied areas. But there is a coordinating activity here, and grant applications received by the Division of Research Grants are assigned either to Environmental Health or to our Institute or to both, with the understanding that they are elegible for possible support by either of us.

BIOLOGICAL POWER SOURCE OF ENERGY FOR ARTIFICIAL ORGANS

Mr. Fogarty. On page 19 you say:

> A practical biological power source to provide energy to artificial organs is urgently needed.

Is that what Dr. Shannon mentioned a while ago?

Dr. Powell. Yes, sir. This relates to a reference I made earlier to the cardiac pacemaker as a notable advance in biologic instrumentation—in this case an electronic device which supports a failing heart. But I would not want to leave the impression that such instruments have already ushered in a new era. I don't think they have, but if we continue to develop artificial substitutes for even partial organ functions they will need power sources. Any external power source has certain inherent complications which I think are obvious. If we can develop power sources which derive their energy from biological processes rather than outside sources, such as a battery, this would permit us to move into this area and would provide power for body functions over an indefinite period of time from natural sources.

FELLOWSHIP PROGRAM

Mr. Fogarty. There is no increase for additional fellowships under your fellowship programs; is that right?

Dr. Powell. That is right. The increase in funds would go for an increase in the size of stipends paid to fellows.

Mr. Fogarty. You show an increase from $35,682,000 to $37,182,000 in training grants but that increase will just about cover increased costs, will it not?

Dr. Powell. Yes,sir.

Mr. Fogarty. Actually, page 33 shows you have five fewer programs in 1965 than in 1964.

Dr. Powell. Yes, sir.

Mr. Fogarty. Would you call that progress?

HOSPITAL COMPUTER PROJECT

Tell us what you are now doing in connection with your hospital computer project under "Collaborative studies" and what your plans are for 1965.

Dr. Powell. The hospital computer project is a project which is operated on contract—actually, two contracts; one to the commercial organization, Bolt, Beranek & Newman, Inc., the other contract to the Massachusetts General Hospital.

The basic purpose of this project is to develop the computer as a tool for research in a clinical setting. Without going into great detail, one might say that if the computer could, with economy of time and effort, provide us with all available information on a patient, this would greatly facilitate clinical research. I would use as a case in point, the halothane study mentioned earlier. This task of determining the precise safety of an anesthetic agent would obviously be much simpler and the answers arrived at much faster if we could feed some of the questions to a computer, rather than go back and review literally hundreds of thousands of patients' records.

It is also recognized that this project would have implications for people with interests other than pure medical research. We are not attempting to limit the project, therefore, solely to things of interest to us but are following the principle that the Institute of General Medical Sciences has an obligation to support programs which are of interest to many program areas of NIH and other bureaus of the Public Health Service.

The computer project has been using commercially available components and has developed a system whereby it is possible to enter patients' records into the computer, or at least a good portion of the patients' records. Within the next few months we are about to embark on a practical test of this, using one ward of the Massachusetts General Hospital as the test area and putting patients' records from that ward into the computer. We expect this experience to provide many derivative uses.

In this project, data being supplied to the computer include results of laboratory tests and patient medication records. It is expected that such information will become more readily available, with a much reduced possibility of error, to the physician treating the patient.

We plan to continue the project in fiscal year 1965, extending the scope of the study gradually within the Massachusetts General Hospital. We have under consideration at this time a proposal to test regional application of computers in hospital research. Obviously, the basic initial cost of this kind of installation is high. If it is feasible, by means of time sharing on the computer, to extend this capability to more than one hospital in a region, the economic advantages will be obvious. Perhaps less obvious are other advantages, such as automatic pooling of data, which would accrue from this operation. Furthermore, a physician in one institution would have immediate access to information about patients in other institutions.

In summary, we think there is great merit in the potentiality of regional utilization of a single computer unit, assuming that our hopes for the basic project are borne out. If they are, we would propose to examine the feasibility of moving to a test of regional applicability.

LIGHT CONVERSION IN PHOTOSYNTHESIS

Mr. FOGARTY. What is this project on light conversion in photosynthesis?

Dr. POWELL. Our research on light conversion in photosynthesis is an ongoing project. It is a very fundamental, very basic study, on the mechanisms by which plants convert light to energy. The project is well along. It was one of the projects which was initially embarked upon as a research grant.

We are continuing this study at present on a contract basis. The projected termination date, I believe, is next year. At that time NIH will reconsider the advisability of continuing support of this project.

FIELD ION MICROSCOPE

With regard to the field ion microscope study, this project has not yet been activated. It is under negotiation at the moment. The purposes are to investigate the feasibility of adapting the field ion microscope to specific biological research. Stated simply, the field ion microscope produces an image by the diversion of a stream of electrons rather than a diversion of a stream of light. Theoretically it is possible with this instrument to obtain much finer resolution, to see much smaller objects, than would be possible with the light transmitting or even with the conventional electronic microscope. More importantly, there are certain simplifications that come from a field ion microscope which may make it a more practical instrument for certain types of biological research.

RESEARCH FACILITIES AND RESOURCES

Mr. FOGARTY. Now we will go on to the "Division of Research Facilities and Resources." On an obligation basis, that is, leaving out the reserve of $613,000, you are asking for an increase of $4,532,000 and this is almost all for research grants, is it?

Dr. STONE. The budget request is for a total of $44,838,000. The increase in the request for 1965 is $4,532,000. This is primarily applied to three programs: The general clinical research centers program where an increase of $539,000 only is requested. This increase will support at least one new center and perhaps a portion of an additional one. I would like to say also that because of nonrecurring costs, in that particular program, we will be able to start perhaps as many as four additional centers with money which is available. This program, as I testified last year, and I emphasize again, is one which is increasing very slowly but, I think, on a highly selective solid basis.

SPECIAL RESEARCH RESOURCES PROGRAM

For the special research resources program, an increase of $2,515,000 has been requested. This will provide continued support to the existing grants. The areas which will be supported include biomedical engineering computer centers and perhaps one enzyme and biopolymer isolation center. The additional remaining funds that are being requested are those for primate centers and the amount here is $1,300,000 which will provide continued support to the operation of the seven established centers—six regional and one national—which have already been supported for a number of years. I think the years are 5 in number. There is a small sum of $39,000 for program increases in review and approval but I assume that you are only interested in the three program areas at this moment.

GENERAL CLINICAL RESEARCH CENTERS

The general clinical research centers are, as you will recall from my testimony last year, those centers which have been established as institutional clinical research resources. I was interested, as I sat here listening, as my colleague, Dr. Powell, explained the "pacemaker" and the dialysis equipment and some of the organ transplantation experiments, to recall that the clinical costs, that is to say the bed costs and other clinical costs, were not completely borne by his research grants. These experiments were carried out in one or another of the general clinical research centers. These are, as used in our terminology, multicategorical. They support the clinical research costs of many of the clinical studies which are related to one or another of the institutes' programs. The general clinical program, as you will recall, had a relatively rapid start, and it has been decided in the last couple of years that it should plateau.

I would not predict at this moment what the ultimate number of centers will be. At the present time, we have approved for funding a total of 73, of which 56 are in operation. The 56 provide for 645 beds. The 73, when they are fully funded and fully in operation, will provide for 914 beds.

SPECIAL RESEARCH RESOURCES CENTER

The special research resources centers provide research support for biomathematical, biostatistical, and for other types of scientific consultation across the whole field of biomedicine, through the 22 or 23 computer centers that we have funded.

It would not be useful at the moment to describe in detail what such a center does because they perform the computation for hundreds of projects through these computer centers.

PRIMATE CENTERS

The primate centers, I expect, will be in full operation in 1 year. That is to say a year from now I hope I can come to this committee and indicate that all seven centers are in operation.

It has been borne in upon me, more forcefully than I was previously aware, the amount of time, and leadtime necessary when one plans a research center of the kind needed for the primate field.

Although the program has started slowly, I think once again the start has been well grounded. All of the centers have research programs going on, though the construction has not been completed.

These projects are carried out mostly in rented labs, elsewhere than on the particular campus that houses the center, in some cases.

That sir, is a justification in support terms, of the $4,532,000 increase that is requested.

METHOD OF FINANCING CENTER PROGRAMS

Mr. FOGARTY. Now, in connection with all these types of centers, is there any requirement for matching or any formal division of cost between the Federal and the non-Federal interests involved?

Dr. STONE. There is no formal requirement for matching on the part of an institution. It is well known, however, that in many cases, our grants do not support the full costs of research as defined by full direct and full indirect costs.

Dr. SHANNON. Mr. Fogarty, I might point out that the only reason we are in this resource program is to add to medical schools certain special and costly resources for which their scientific talents and the general research environment promise most effective use. I point out, in each of these cases, that these are specific resources that bear no relationship whatsoever to the general stream of education but relate to highly sophisticated and very costly—but also very essential—types of research.

The centers, the research resources, and the special resources, such as computers—I see no way of conducting programs of this sort on a cost-sharing basis, with the institution picking up a substantial amount of the cost. I think it is true, as Dr. Stone points out, that there is some grantee participation, particularly in terms of salaries; also the ancillary input to these centers is at the cost of the university. But basically these centers have been developed as an essential NIH contribution to assure that the entire gamut of biomedical research is made more effective.

Mr. FOGARTY. And now Dr. Stone in closing what about the general research support grants?

Dr. STONE. The general research support grants program for which $40 million has been requested is supported through a percentage of the appropriations for extramural research projects from each of the several institutes. This is done in accordance with section 301d of the Public Health Service Act where special authority is provided by the Surgeon General for this particular program.

General research support funds provide institutions with an increased measure of freedom and responsibility for allocating a part of the Federal funds locally available for the support of health-related research. This permits institutions an increased measure of control over the quality, emphasis, and direction of their own research activities: institutions are enabled quickly to redress program imbalances without restriction as to specific scientific problems, discipline and disease entities; funds can be utilized flexibly, so as to meet different needs year by year, and catalytically, so that other forms of support, non-Federal as well as Federal, are engaged promptly and efficiently, as soon as any given research activity reaches maturity. General research support permits institutions to reap maximum advantages through local insight into the best means to identify and support research excellence among emergent research ideas and techniques provided by the faculty and staff.

Office of International Research

Mr. Fogarty. Now, Dr. Kidd, the Office of International Research. You did not come out very well. Was this budget arrived at before you took command?

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH

Dr. Kidd. Mr. Chairman, the major element of the budget comprises the International Centers for Medical Research. These ICMRT's are budgeted in 1965 at the same level as 1964. That is $3 million. This sum is financing, at the moment, five centers in various parts of the world, and over the past year the effort has been to extend the scientific breadth of the work that is undertaken in these centers and to solidify the positions established. In our judgment, this period of consolidation is one that does not warrant at this time an expansion of the budget for these organizations.

Now, there is one other program that is directly administered.

Mr. Fogarty. This seems to be the same defense all the way through the NIH.

Who thought up this idea of consolidation as an excuse for not expanding?

Dr. Kidd. I would not know about the remainder of the Public Health Service but I think for these centers this is an objective statement of fact. These are quite complicated organizations to establish. They all have the problems of operating in a new environment; the transfer of personnel from the United States abroad; the establishment of rapport with the people in the host institution and the host country. It is simply not a program that can effectively move ahead rapidly.

Mr. Fogarty. It is not much of a program the way it is.

Dr. Kidd. There is under consideration for the next stage of expansion of this program, if it were to expand, the establishment of a center in Africa; for the time being, we have our hands full with the five that are now in operation.

Mr. Fogarty. What are the five?

Dr. Kidd. Johns Hopkins is associated with the All-India Institute of Hygiene and Public Health in Calcutta.

The University of California has establised close relationships with the Institute for Medical Research in Malaya in Kuala Lumpur.

Tulane is working with the University del Valle in Colombia.

Louisiana State has established a working relationship with the University of Costa Rica.

Finally, Maryland has established an ICMRT in conjunction with the Institute of Hygiene in Lahore, India. Those are the five operations.

Mr. Fogarty. Where is this place in India?

Dr. Kidd. Lahore.

Dr. Shannon. It is north of Karachi.

Mr. Fogarty. Oh, in that area.

Dr. Shannon. About 400 or 500 miles north.

Mr. Fogarty. Now, the total increase in this omnibus appropriation item is over $10 million and you get $95,000 or less than 1 percent.

I would not be very happy about that if I were in your position.

Dr. Kidd. Well, I explained the ICMRT's.

INTERNATIONAL POSTDOCTORAL FELLOWSHIP PROGRAM

The other major program element is the international postdoctoral fellowship program. That is held constant at $1.2 million, providing for 140 to 145 postdoctoral fellowships from abroad for people who come to study in this country.

The program is extremely productive. It is well received, and not only outside the United States. These people that come here are in effect the cream of the younger crop of investigators from around the world and they contribute substantially to research within the United States. These awards are very highly competitive in the home countries.

INTERNATIONAL CENTERS

Mr. FOGARTY. From what I heard, these international centers are working out pretty good.

Dr. KIDD. Yes; they are. They vary quite widely. Some of the universities have had great success in getting senior faculty members to go abroad. The rate of development has differed, but by and large, the basic concept is being carried out. That is, use of grant funds for the establishment of a continuing long-range relationship between a major university in this country and a major university abroad. The result is to pair the resources at home with the resources abroad. It is particularly important to provide an environment and a structure within which faculty members from this country can work abroad without losing their academic status and seniority within the United States. This has been a major problem in, I think, virtually all attempts to carry on biomedical research outside of the United States, with academic people, and the ICMRT's are a way of solving the problem.

Mr. FOGARTY. How much of an increase are you requesting?

Dr. KIDD. For the total?

Mr. FOGARTY. The international centers.

Dr. KIDD. No increase whatever; $3 million in 1964, and $3 million in 1965.

Mr. FOGARTY. That is not even holding your own, if you have the same in 1965 that you had in 1964.

Dr. SHANNON. I would like to make two comments on it.

One, the decision to hold to the $3 million is not Dr. Kidd's nor is it the Department's, nor the Public Health Service. It is mine, so I will bear the brunt of your criticism.

It is my conviction that these are so complex that before we establish more, we have to know how the concept works. This year is too early to say.

Now, for the first time, we have a capability of having topflight investigators who have access to populations for special studies that cannot be done in this country. Now, if they need expansion of their budget activities, this can be done within the regular grant program. Those who wish to work in that area can apply for a grant and be fully supported in the activity.

So I would rather let the people compete in the open market for these grants rather than put these funds in a protected category and remove them from competition with scientists who will do their work domestically. I view the $3 million as the smallest amount that is adequate for the moment, at the present stage of development, to provide a very stable base—both in the university in this country and in the field—which can grow or not depending upon the excellence the program demonstrates. Next year we will take a very hard look to determine what program impact there is, and select the right type of mechanism for the long-term support.

FOREIGN FELLOWSHIP PROGRAM

Mr. FOGARTY. Tell us about your foreign fellowship program. How it benefits us, as well as foreign countries.

Dr. KIDD. These foreign fellows are selected at the post doctoral level; that is, they have completed virtually all of their academic training in foreign countries. They are selected, as I said, on a highly competitive basis, by boards that we have set up in some 40 countries outside of the United States. These people, by and large, are the best equipped products of foreign countries. They are outstanding people. Competition for awards is extremely stiff, and it is considered an honor to secure one of these fellowships.

The people who come here are directed to, or they select themselves, laboratories, to which they come. The fellows, particularly from the countries in Western Europe, come as full collaborators and bring with them techniques that are new to this country. They contribute a high degree of intelligence to the laboratories here, and they establish collaborative relationship with the laboratories in which they work when they return home.

Mr. FOGARTY. All right. How much of an increase are you requesting?

Dr. KIDD. There is no increase requested for this. It was $1.2 million for 1964 and $1.2 million for 1965.

Mr. FOGARTY. Are these fellowships granted just for advanced study in American schools?

Dr. KIDD. Yes; only in American schools. The fellows come from a foreign country to laboratories within this country.

INTERNATIONAL RESEARCH

Mr. FOGARTY. What little increase you have is in the activity "International research." Would you tell us what you are doing and what the increase is for?

Dr. KIDD. That is right. Over the last year, we have been confronted with essentially two tasks that required this increase. First, outside of the United States, we have offices in Paris, London——

Mr. FOGARTY. Are those the five field offices you mentioned in the justifications?

Dr. KIDD. The five foreign field offices plus the staff at Bethesda.

The foreign staff has had the problem of securing for us a number of different kinds of data. The first relates to medical research expenditures outside of the United States. By and large, this has been information that has been unavailable until recently, and as a consequence, we have had some difficulty in knowing what precisely the role of the U.S. expenditure has been.

We have had difficulty finding the investment that other countries have been making in medical research and how that investment has been changing over the years. Our offices have had the task of securing this data as a baseline for policy determinations.

In addition to that, they have had quite heavy reporting loads on two subjects. First, the status of individual grants, and second, general policy and structural developments in other countries. They have had the task of keeping us informed of what is happening not only to the national budgets, but also the changes in structure of research councils and other matter that affect our dealings with foreign countries.

Mr. FOGARTY. Where are these five foreign field offices and how big are they? What activities are carried out there?

Dr. KIDD. The largest office is the one in Paris. It consists of two professionals, and all of these offices are quite small as a matter of fact. The Paris office has the responsibility of dealing with all of the countries of Western Europe except the United Kingdom. We have an office in London, with one professional and a secretary.

Then, in New Delhi, we have an office with one professional, and in Tokyo an office with one professional, and in Rio, an office with two professionals. By and large, the functions of these offices are identical. The functions, to summarize, are the reporting function and the analytical function which provides both general information and data on individual grants.

INTERNATIONAL RESEARCH CAREER DEVELOPMENT

Mr. FOGARTY. Now, will you briefly describe the international research career development program you started last year and tell us how you think it is working out.

Dr. KIDD. This program was designed essentially to provide the Public Health Service with a somewhat larger group of people, who will have direct experience in working in research environments outside of the United States.

The essentional rationale of this program rests on the assumption that the Public Health Service will be dealing with other countries for the indefinite future in research, and that it would be to the advantage of the Service to have people who have had tours of duty and firsthand work in laboratories outside of the United States.

The program is working well. There have been some problems inaugurating it, arising out of two circumstances. The first is that the leadtime on recruitment is quite long for these people. We have to recruit them approximately a year in advance in order to make all the arrangements for their work outside of the United States.

Second, the problem has been that these people work in U.S. Government installations. These are young fellows who are fulfilling their military obligations, and we feel that we can operate this program only if they are performing a direct service to the United States, which means service in a U.S. installation. There are not, actually, too many U.S. medical research installations outside of the United States and as a consequence we feel that we will attain a level of approximately 10 in this program during the coming fiscal year, and will remain at about that level. I would suspect that this will never be a large program, because a large program is not indicated by these objectives, which is to supply a stream of people—not too large—but adequate, who have the sort of experience necessary.

Mr. FOGARTY. What was your assignment overseas?

Dr. KIDD. I worked for a year in Geneva in 1958 and 1959 with the World Health Organization, just after the United States had given the World Health Organization a planning grant for the establishment of a medical research training program. My job there was to assist them in laying out fields of research; setting priorities; establishing procedures and guidelines and the writing of background material for the consideration of the Director General and of the WHO Advisory Committee on Medical Research. Dr. Shannon has been a member of that Committee until recently.

SHORTAGE AREAS IN BUDGET

Mr. FOGARTY. That is why I am surprised; with all that experience and background, you come in here and say you are satisfied and happy with this budget that you have to operate with in 1965.

Dr. KIDD. Well, I am not entirely satisfied with it, if I could speak as an individual.

Mr. FOGARTY. You would not have said this 2 or 3 years ago, I am sure.

Dr. KIDD. As an individual, there are areas in these programs with which I am not satisfied.

Mr. FOGARTY. I am asking you to speak up now as an individual. Give us your best judgment.

Dr. KIDD. Well, my judgment is that so far as international fellowships are concerned, this area of activity could be substantially expanded to the benefit of the United States, because essentially, these people are, as I said, a very highly selected group; they are intellectual leaders, so to speak. They are, predictably, the leaders of science for the future around the world in the biomedical field.

Many, predictably, with this high degree of competition, are going to become not only excellent scientists, but leaders in their countries; leaders of medical education and leaders of research.

In fact, this is a highly productive program, and in this country I think we benefit substantially from the presence of these highly intelligent young people from outside the United States.

Mr. FOGARTY. Isn't this whole international research program a good way of making friends in other countries?

Dr. KIDD. I think it is.

Mr. FOGARTY. Rather than giving them handouts?

Dr. KIDD. It is certainly an area of activity in which the United States has attained world leadership; not necessarily because of the international programs as such, but the whole vigor of the United States has placed this country in the forefront of the world.

INCREASED INTERNATIONAL INTEREST IN MEDICAL RESEARCH

Mr. FOGARTY. It seems to me I hear more about international medical societies every year in such areas as cancer and heart.

Dr. KIDD. Not only medical societies, but additional countries every year are establishing governmental bodies concerned with medical research. They are establishing medical research councils and other organizations designed to expand this area of effort as a governmental activity.

As a matter of fact, we were a little bit worried 2 or 3 years ago when the NIH expenditures outside of the United States were increasing quite rapidly, that this would result in the United States taking over the financial obligation that might be borne by other countries.

It is now clear that the opposite has happened. This new U.S. investment has served as a stimulus to other countries. As we go around and talk with the people in government and the universities, country by country, they spontaneously say that the investment of this money by the United States has not shifted a burden to this country but has instead resulted in a marked expansion, particularly in the advanced countries, in the medical research effort of their own nations. So that this has served as an incentive to strengthening of medical research in those parts of the world that do conduct the major world programs in medical and biological research.

Mr. FOGARTY. Well, England is one of the leading countries, isn't it?

Dr. KIDD. Well, England is one of these. Canada is another one. You alluded this morning to this question of the decline from $8.5 million in these advanced countries. We have been talking in some detail with the representatives of each of these countries. After this period of stimulus which has gone on to date, the momentum is such, say, in Canada, that the expansion in their medical research budget will exceed the decrease that will come about as a result of a roughly 20 percent contraction of NIH funds during fiscal year 1965.

Mr. FOGARTY. I did not think it was that much in Canada. I thought they were not too liberal with their funds in the area of medical research. In the mental retardation field, they have hardly anything, I thought.

Dr. KIDD. I don't know about the specific areas. With respect to the total budget of medical research through the Medical Research Council, it is going up quite substantially.

Mr. FOGARTY. If it is going up from zero, anything would be substantial, would it not?

Dr. KIDD. In absolute terms, their increase will be about $1.7 million which is about a 20-percent increase.

Mr. FOGARTY. What are some of the other leading countries?

Dr. KIDD. England, France, Sweden.

Take the Swedish experience. Professor Gustaffson, who is the chairman of their Medical Research Council, and Professor Rexed, the scientific adviser to the Prime Minister, have told us that they can absorb through Swedish resources a moderate decline in PHS grant support, if we give them advance notice.

Now, our interest, as I see it nationally, is not to support research per se with U.S. funds outside of the United States. It is rather to see that research is done outside of the United States which is of value to the United States domestically, and not necessarily with funds from the United States.

Mr. FOGARTY. What about Italy?

The reason I ask, I accompanied Dr. Terry last year, and spent 3 days down there. I thought Dr. Terry was quite impressed with some of the research people they had working in Rome and other cities.

Dr. KIDD. Italy of course is poorer than Sweden; it is poorer than France. Nevertheless, they have had a resurgence of research support over the past 3 or 4 years that is quite remarkable.

Mr. FOGARTY. They have some Nobel prize winners.

Dr. KIDD. Yes, they do. Chain and Bovet.

Mr. Fogarty. We met both of them. We spent the morning with Dr. Chain and the afternoon with Dr. Bovet.

Dr. Kidd. Now, the situation with respect to biomedical research from domestic resources in Italy is not as favorable as in, say, Sweden.

Mr. Fogarty. What was that again?

Dr. Kidd. The economic situation in Italy is improving but their capacity to support biomedical research is not as great as is the case say in Sweden or in France. They have had an increase, but, as you indicated, it has been from a low base. In that connection, in this decline of PHS grant expenditures from $8.4 million in 1964 to $7 million for Western Europe in 1965, our guidelines are that this is a global figure that is applicable to Canada, Western Europe, United Kingdom, Australia, and New Zealand. We are reviewing the situation in each country to see how the total should be distributed. We do not necessarily simply apply an arithmetical formula uniformly to each country. The funds are allocated in accordance with our program needs, the quality of the research to be done, and the economic capacity of the countries to absorb the increase.

Mr. Fogarty. Mr. Denton?

FINANCING OVERSEA ACTIVITIES

Mr. Denton. I believe that you asked for $3 million for maintaining the agencies overseas, is that right?

Dr. Kidd. That $3 million, Mr. Denton, is for the support of these five operations involving a U.S. university with a foreign university—the so-called ICMRT's.

Mr. Denton. The one in India was with Johns Hopkins?

Dr. Kidd. Yes, sir.

Mr. Denton. California and who?

Dr. Kidd. California and the Institute for Medical Research in Malaya—in Kuala Lumpur, Malaya.

Mr. Denton. How does that work out? Do they do research in those foreign countries, and we pay them for it? Is that it?

Dr. Kidd. The relationship is a dual one.

First, each university in this country establishes a base here—an organization within the faculty, a group of people who are interested in working abroad. Then, outside the United States, in Kuala Lumpur or in Calcutta, as the case may be, they establish a base composed of faculty members from this country who go abroad. They then work in association with the people from the foreign university.

Mr. Denton. I can see why you need to pay out appropriated funds in this country, but when you get to India or Malaya, why are they not paid out of the 480 funds, or counterpart funds?

Dr. Kidd. Now, I actually don't know with respect to India, what the arrangement is for the use of Public Law 480 funds, under the ICMRT program.

Mr. Denton. There is a lot of money in India. There should be anyhow.

Dr. Shannon. I can answer that specifically. We have not been able to get agreement for the expenditure of Public Law 480 funds in India through the Ministry of Health. This is beyond us. Quite the contrary, in Pakistan, we don't enter this type of negotiation at all.

Mr. DENTON. I thought they agreed the 480 funds could be used for that.

Dr. SHANNON. They are used for other purposes, but the Indians have not agreed to use them for support of medical science; and for the use of so-called U.S. currencies, there must be agreement as to the purpose to be served.

Mr. DENTON. Of course, the act provides they should be used for certain purposes, of which this is one.

What about Malaya then? They have funds there.

Dr. SHANNON. I would be glad to give you a very specific report on that; where Public Law 480 funds are available to ourselves, they are used. Now, there are a whole variety of U.S.-owned currencies in many of these countries—counterpart funds as such are quite different from Public Law 480 funds, as such.

Mr. DENTON. That is right.

Dr. SHANNON. Right at the moment, I do not know the specific situation.

Mr. DENTON. Of course, the Americans have a great deal of money in the counterpart funds, other than the 480.

Dr. SHANNON. That is right.

Mr. DENTON. I cannot think of one of those countries that you mentioned that does not have funds of that kind.

Dr. SHANNON. Well, in Pakistan we used Public Law 480 funds very extensively. In India we use Public Law 480 funds in many projects, but the general economic situation is such that the Indian Government does not want to use much of this currency.

Dr. DENTON. It seems to me that when we have a balance of payment against us, bad as it is, and we have those funds in those foreign countries, we should not be sending moneys to the foreign countries for two reasons.

First, we ought to use those funds instead of taking money out of this country. It adversely affects the balance of payments.

Dr. SHANNON. Yes, sir. I could not agree more, Mr. Denton. We are not in a determining position on this.

Mr. DENTON. Now about these five. One of them was in New Delhi; another one was in Tokyo.

Now, I think those should not be paid from——

Dr. SHANNON. There are no Public Law 480 funds available to us in Japan.

Mr. DENTON. No 480, but there are counterpart funds.

Dr. SHANNON. We ought to have legal authority to use those funds? Is that what you are saying?

Mr. KELLY. It is my understanding, in connection with the foreign currency research program, we can only use Public Law 480 funds; but it is also my understanding we made an arrangement with the Treasury Department that when we made payments to support a research undertaking, in a foreign country, that they were to utilize to the extent available, any U.S.-owned foreign currencies, and only to make the payment in dollars when there were no U.S. foreign currencies available to carry out the program.

Mr. DENTON. You have an agreement with the Treasury Department?

Mr. KELLY. Yes, sir.

Mr. DENTON. It is carried out in that way?

Mr. KELLY. Yes, sir.

Dr. KIDD. We routinely check on the availability.

Dr. SHANNON. I can point out—I was not viewing it precisely in that light—but in extension to what Mr. Kelly said, approximately 90 percent of the funds that support research in Israel are through U.S.-owned currency which is purchased in this country in dollars.

Mr. DENTON. Just one last question.

ORGANIZATION FOR ADMINISTRATION OF PRIMATE CENTERS

I don't understand why the primate centers and these general centers and these new pharmacological and toxicological centers are under your agency.

Dr. SHANNON. The resource centers?

Mr. DENTON. Yes. I thought these primate centers, for instance, were used for categorical diseases.

Dr. SHANNON. They are, sir, but because they are used by a whole number of programs, it has been simpler, administratively, to run under one accounting point; under one series of guidelines; and under one series of regulations.

Mr. DENTON. I see. That is all.

ORGANIZATION OF TOXICOLOGICAL CENTERS

Mr. LESINSKI. Dr. Kidd, I commend you on your passion of correlating your activities, because I think it is practical. I have tried to get that through to Dr. Shannon as far as catching them all—the 17 or 18 different programs, cancer and the like. I think it is extremely unwise to be operating in a field in that vein, and I still must insist, and I do so today, that my point will be brought across that Dr. Shannon should reinvestigate his thinking. Regarding Environmental Health, why should there be more than one center?

Mr. KELLY. Are you referring to toxicological centers?

Mr. LESINSKI. That is right. Why not start with one center, and then expand it from there, instead of going out with four or five or six or seven at the same time.

Dr. SHANNON. I think this could be done, sir, but I think you would end up with such a large activity as to be a very cumbersome one to operate, and one that would be limited in its access to the variety of scientific attitudes and scientific points of view.

Mr. LESINSKI. Why can you not place it in an area of industrial activity, like around Detroit, Pittsburgh, or Cleveland or some area like that, where you have the various components of industry and farming? You have the problem of fertilizers, and pesticides getting into water. You have the problem of various chemicals getting into water. You have the problems of air pollution and water pollution, by industry, and so forth. Why can you not operate one overall center?

Dr. SHANNON. I think you could but it would be my judgment that drawing, as you would, on the limited resources in such a community because there are relatively few people in any community with special knowledge in these areas, that scientific progress from a single center would be less than the scientific progress that would be derivable from the limited number of centers. I am not talking about large numbers. I am talking about three, four, five where they drew on the scientific talent of a number of university groups rather than one.

Mr. LESINSKI. The University of Michigan would be very glad to accommodate you if you want. That is your decision to make, but it seems to me you always think in a global or spherical thinking, you might say, like the stars, way up there, instead of getting down to a specific thing here. You are thinking in a realm of unreality by just circumventing everything. I don't understand what you are trying to attempt.

Dr. SHANNON. I am trying to develop a hard-hitting program, sir, to the best of my capabilities. If you don't feel I can do it, then I think you ought to talk to the Surgeon General and have me removed.

Mr. LESINSKI. That is not the point.

Dr. SHANNON. I think it is the point.

Mr. LESINSKI. The point being that you seem to be thinking the more money you spend, the more people you have working for you——

Mr. FOGARTY. I don't think he is spending enough.

Dr. SHANNON. You reach a different conclusion than I do from my action, sir. I think that if there is any term that I would use to characterize my action, I would say I am not an expansionist.

Mr. LESINSKI. I like to hear that. I am glad to hear that statement.

Dr. SHANNON. You don't believe it, sir, I am sure.

Mr. LESINSKI. I mean, you don't in this area. You are talking about the departmental health; about the various toxics in the air, and so forth. The effect upon human life, which I agree with to a great degree. In my dissertation about this point before the Food and Drug can hardly pass upon so many of these various drugs and pills and so on, I agree with you on that point, and I have to agree with you that there is so much development today and so many new drugs on the market, no one knows what the score is.

ENVIRONMENTAL ASPECTS OF TOXICOLOGY

Dr. SHANNON. Could I talk about the environmental aspect of this toxicology a moment? Let me point out how different this is from some of the others. This has been developed by the Bureau of State Services. This program is not my responsibility. I am intimately concerned with its evolution, however.

The first thing that the Bureau of State Services has to do in trying to catch hold and get control of problems of insecticides, economic poisonings, and chemical intoxicants in general, is to see what the hazard is today. This means using sampling techniques in analysis of such things as fats, foods, soils, and water. They must determine what those things are that we have done during the past 10 years that already constitute a hazard.

This involves a fairly extensive field operation and a fairly extensive chemical operation, because the chemical methodology is to determine the concentration of these substances in soil and food and animal life. They then have to study the broad problem of the phenomenon called biological concentration.

Let me give you an example of what I mean. When you throw, say, insecticides on the field, a certain number of these insecticides are preferentially localized in certain areas of the plant, which in turn, is the foodstuff of certain animals. Furthermore, certain of these insecticides are concentrated in rodents, or other animal life in the field which in turn, are fed upon by other animals. This brings further concentration. So you have to study the total locality of different areas relating to soil, to drainage, to the amount of animal population in relation to the farm animals, the wild animals, and the material the area grows, and its effects on animal husbandry quite apart from its effects on human life.

Then you have to go further and study the uptake from the animal tissues that are consumed by humans, either directly as meats, or in milk or allied substances. Having done that you have the broad problem of determining in much more precise fashion than we know now, how the animal body handles these foreign substances.

Now, the hydrochlorides, starting with DDT, have unfortunately a characteristic that they are not metabolized by the body but tend to be retained in the body for indefinite periods of time. These are stored primarily in the fat reservoirs of the body; and the best way one can determine the amount of exposure one has had over the years is to do a chemical analysis on tissue looking for these contaminants. But we also know these materials go into the nervous system. It is in this way that insecticides or similar pollutants give rise to problems in medicine, problems in agriculture, problems in animal husbandry, in an entire mixture.

Now, all I would say is that these are sequential problems, which are probably too great to concentrate in a single place, and furthermore, since the agricultural practices of different areas of the country are different, since the plant and animal life is different in different parts of the country, it would not be wise to put all one's eggs in the Detroit basket or the Madison basket or some other basket. There are different problems of rainfall; different problems of soil drainage; a whole variety of factors. So it would be necessary to study these in their natural habitats. This is the way the problem must be worked out. There are many things that determine the correlation between the use of insecticides on the one hand and toxicity to the human population on the other.

Mr. LESINSKI. In all due respect, I concur with your statement. Of course, you would have to have a small office in the Northwest, where you have the matter of sulfuric acid in the streams from pulpmills. I agree with you on that point, because the environment is different; the problem is different; but a small office is sufficient for that. Why a great big office? You should have to have an office someplace, I have to concur with you, to correlate these various findings. You have to have that. Why have five or six big ones? I just cannot comprehend it.

Dr. SHANNON. To the best of my judgment, in order to get to this scientific problem, it will require setting up a limited number of laboratories, in geographically dispersed areas, perhaps three or five. If you recall, I said also that this is a problem that has to be managed. It would be my best judgment that what we need here is a semi-industrial-type laboratory, run by contract rather than by grant.

I think this is one of the areas where you and I would see eye to eye; at least in terms of how the substance of the program would be managed.

Mr. LESINSKI. Definitely.

Dr. SHANNON. But we do not see eye to eye on whether this can be done in one place; in one very large operation, or done better in multiple, dispersed operations.

Mr. LESINSKI. Why did you then change your mind about the original thinking of putting the Environmental Health Center here in Washington?

Dr. SHANNON. Mr. Lesinski, this is not part of the NIH operation at all. This is part of the Bureau of State Services, where they will address themselves to a whole array of tasks. It will involve the whole area of environmental health.

Mr. KELLY. We will address ourselves to the environmental health facilities when we take up the "Building and Facilities" account.

Dr. SHANNON. We are dealing with a very small area that impinges on environmental health activities, and will, of course, have to be correlated and coordinated with them by the Public Health Service. We are dealing with the point where environmental chemical toxicants move over into the area of drug intoxicants.

Mr. LESINSKI. I am in full accord with your basic attempt to find out what the various relations of toxicities are on the human body. This is very important to all of us. I cannot argue with you on that. The only thing I am concerned about is you are going at it with a shotgun approach, which I am opposed to.

Dr. SHANNON. Sir, I don't think our approach is shotgun.

Mr. LESINSKI. I certainly hope not. I have had some static on supporting your position, but on the other hand, I am also recognizing the fact that you can achieve results with funds in these studies and I want to say this: If you need any help in anything, to get it going, I am with you 100 percent. How far I want to go is another thing.

GRANTS FOR CONSTRUCTION OF HEALTH RESEARCH FACILITIES

WITNESSES

DR. FREDERICK L. STONE, CHIEF, DIVISION OF RESEARCH FACILITIES AND RESOURCES
DR. JAMES A. SHANNON, DIRECTOR, NIH
GORDON J. KLOVDAHL, EXECUTIVE OFFICER, DIVISION OF RESEARCH FACILITIES AND RESOURCES
B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NIH

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
Grants:			
1. Health research facilities	50,000	50,003	50,000
2. Centers for research on mental retardation			8,000
Total program costs, funded—obligations (object class 41)	50,002	50,003	58,000
Financing:			
Unobligated balance brought forward	−5	−3	
Unobligated balance carried forward	3		
New obligational authority (appropriation)	50,000	50,000	58,000

INCREASE FOR 1965

Mr. DENTON. We will now take up "Grants for construction of health research facilities." The appropriation for 1964 is $56 million and the request for 1965 is $58 million. The $2 million increase is for centers of research on mental retardation. Is that right?

Dr. STONE. This appropriation comes to you as a result of two pieces of legislation. Fifty million dollars is legally mandated under title VII, part A of the Public Health Service Act and in 1964 an additional sum of $6 million is made possible by the addition to title VII of part D of the act. The act also provides that under part D, title VII, the second year of the program; that is to say, in 1965, the sum of money which may be appropriated is $8 million. That, sir, is how we get from $56 to $58 million. You are quite right, the extra $2 million requested under the budget will be used for mental retardation center construction.

DEMAND UNDER THE FACILITIES ACT OF 1956

Mr. DENTON. You say this estimate includes $50 million, the maximum authorization for construction under the Health Research Facilities Act of 1956.

Dr. STONE. Yes, sir.

Mr. DENTON. Now, how much do you estimate would be required in 1965 if you funded all of those projects?

Dr. STONE. Something clearly in excess of $100 million. It will be between $100 and $150 million. I cannot make it more accurate than that for the simple reason that I do not yet know the effect on health research facilities of a new piece of legislation, Public Law 88-129, the Health Professions Educational Assistance Act. That act has hepled to generate a tremendous application intake in our program for additional research facilities construction. The total needed for funding will clearly be in the area of $100 million plus, for approved applications recommended to the Surgeon General for award.

INDICATION OF NEED FOR MENTAL RETARDATION RESEARCH CENTERS

Mr. DENTON. $8 million of the request is for the mental retardation research centers. What indication of the need and demand for these funds do you have?

Dr. STONE. The indication is very specific, sir. At the present time we have three applications, two of which we have reviewed, and they come to a total of $11 million, as approved. An additional application, which is about to be received, requests another $4 million. We have, furthermore, something in the order of 8 to 10 applications, with which I am intimately familiar, expected between now and the beginning of fiscal year 1965 that will total close to $30 million for mental retardation research construction.

ELIGIBILITY, MATCHING, AND ALLOCATION OF FUNDS

Mr. DENTON. Would you place in the record a statement for both of these programs, setting forth the eligibility requirements, the method of allocating the funds, and the matching requirements?

Dr. STONE. Yes, sir.

(The statement is as follows:)

HEALTH RESEARCH FACILITIES

Eligibility requirements

The applicant must be a public or nonprofit institution determined by the Surgeon General, after consultation with the Council, to be competent to engage in the type of research for which the facility is to be constructed.

The application must contain or be supported by reasonable assurances that (1) for not less than 10 years after completion of construction the facility will be used for the purposes of research, or research and related purposes, in the sciences related to health for which it is to be constructed, (2) sufficient funds will be available to meet the non-Federal share of the cost of constructing the facility, (3) sufficient funds will be available, when construction is completed, for effective use of the facility for research, or research and related purposes, for which it is being constructed, and (4) the proposed construction will expand the applicant's capacity for research in the sciences related to health, or is necessary to maintain the quality of the applicant's research in the sciences related to health.

Method of allocating funds

The Council and the Surgeon General shall take into consideration the relative effectiveness of the proposed facilities in expanding capacity for research, or research and related purposes, in the sciences related to health, in improving the quality of such research or related purposes and in promoting an equitable geographical distribution of such research (giving due consideration to population, available scientific research workers, and available research resources in various areas of the Nation).

Matching requirements

The amount of any grant for health research facilities shall be that recommended by the Council or such lesser amount as the Surgeon General determines to be appropriate except that in no event may such amount exceed 50 percent of the necessary cost of the construction of such facility to be used for research, or research and purposes related thereto in the sciences related to health, or, in the case of any other multipurpose facility, 50 percent of the part of the necessary cost of construction which the Surgeon General determines to be proportionate to the contemplated use of the facility for research or research and related purposes, in the sciences related to health.

MENTAL RETARDATION RESEARCH CENTERS

Eligibility requirements

The applicant must be a public or nonprofit institution which the Surgeon General determines is competent to engage in the type of research for which the facility is to be constructed; and the application contains or is supported by reasonable assurances that (1) for not less than 20 years after completion of construction, the facility will be used for the research, or research and related purposes for which it was constructed, (2) sufficient funds will be available for meeting the non-Federal share of the cost of constructing the facility, and (3) sufficient funds will be available, when construction is completed for effective use of the facility for the research or research and related purposes, for which it was constructed.

Method of allocating funds

The Surgeon General shall take into consideration the relative effectiveness of the proposed facilities in expanding the Nation's capacity for research and related purposes in the field of mental retardation and related aspects of human development, and such other factors as he, after consultation with the National Advisory Council or councils concerned with the field or fields of research involved, may by regulation prescribed in order to assure that the facilities constructed with such grants, severally and together, will best serve the purpose of advancing scientific knowledge pertaining to mental retardation and related aspects of human development.

Matching requirements

The total of the grants with respect to any project for the construction of a facility under this part may not exceed 75 percent of the necessary cost of construction of the center as determined by the Surgeon General.

Mr. DENTON. Is there anything else you want to say about this?

Dr. STONE. No, sir. I have nothing more to say, sir.

Mr. DENTON. All right. Thank you.

BIOLOGICS STANDARDS

WITNESSES

DR. RODERICK MURRAY, DIRECTOR, DIVISION OF BIOLOGICS STANDARDS

DR. JAMES A. SHANNON, DIRECTOR, NIH

DR. C. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS, NIH

GEORGE A. BRUST, EXECUTIVE OFFICER, DIVISION OF BIOLOGICS STANDARDS

MISS ELIZABETH HENNIGAN, BUDGET OFFICER, DIVISION OF BIOLOGICS STANDARDS

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NIH

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
11 Personnel compensation:			
Permanent positions	1,405	1,781	1,918
Positions other than permanent	18	25	25
Other personnel compensation	65	78	74
Total personnel compensation	1,488	1,884	2,017
12 Personnel benefits	143	183	192
21 Travel and transportation of persons	99	99	103
22 Transportation of things	9	6	6
23 Rent, communications, and utilities	42	44	47
24 Printing and reproduction	2	5	5
25 Other services	162	673	686
Payment to National Institutes of Health management fund	748	845	845
26 Supplies and materials	661	908	919
31 Equipment	169	170	172
Total obligations	3,523	4,817	4,992

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	235	294	299
Full-time equivalent of other positions	4	5	5
Average number of all employees	221	260	264
Employees in permanent positions, end of year	219	268	273
Employees in other positions, end of year	12	9	9
Average GS grade	7.0	7.4	7.5
Average GS salary	$6,425	$6,985	$7,065
Average salary of ungraded positions	$4,203	$4,137	$4,137

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities: Biologics standards (costs—obligations) [1] [2]	3,523	4,817	4,992
Financing: Comparative transfer from other accounts	−3,523		
New obligational authority		4,817	4,992
New obligational authority:			
Appropriation		4,787	4,992
Proposed transfer from "National Heart Institute" due to the Uniformed Services Pay Act of 1963		30	

[1] Includes capital outlay as follows: 1963, $135,000; 1964, $170,000; 1965, $172,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $85,000 (1963 adjustments, −$85,000).

Mr. DENTON. Do you have a statement, Dr. Murray?

Dr. MURRAY. We have a prepared statement.

Mr. DENTON. Would you put it in the record, please?

(The statement follows:)

Mr. Chairman and members of the committee, the Division of Biologics Standards is, as you know, responsible for administering the biological control provisions of the Public Health Service Act. This involves a system of licensing which is based on the review of manufacturing records, the inspection of physical facilities of manufacturers, as well as actual testing of the products in its own laboratories.

A biological product, such as a vaccine or serum, is a complex biological material frequently prepared from pathogenic or potentially pathogenic organisms. The staff required to perform this control function must include scientists with special training in medicine, microbiology, and associated sciences. These scientists must also pursue a program of research concerned with their particular field of interest and responsibility so that the Division can maintain a position of knowledge and leadership in the entire field of biologics control.

Recently adopted regulations call for the monitoring of trials of new drugs under clinical investigation. The Division must therefore maintain surveillance of such studies in progress on biological products which would be subject to licensing under the provisions of the Public Health Service Act.

New vaccines and other therapeutic or prophylactic materials arising from new discoveries as to the cause, prevention, or treatment of infectious diseases such as measles, hepatitis, rubella, or diseases caused by respiratory viruses, arbor viruses, etc., can be expected. In anticipation of this, it is necessary to recruit personnel skilled in these areas and to mount corresponding programs of research.

It is also necessary that increased efforts be given to certain basic divisionwide responsibilities in implementation of the control of biological products. Accordingly, it is proposed to increase efforts in the development of requirements and regulations particularly for new products; that is, to formalize the criteria and standards for licensing for an increasing number of products.

With the upsurge in the development of new products and the increasing use of standard preparations and standard methodology for their use, it is necessary to increase the professional staff for the investigation of newer methods and techniques of processing, storing, and systematic replacement of existing standards and reference preparations as well as the development of new preparations to be used in this way.

Although it has been stated previously, we believe that it is appropriate to note again that although newly developed products create the heaviest and most urgent demands on the Division, problems often arise concerning long-established products. For this reason, the Division must continue to maintain an active interest in areas of research which are no longer of primary concern to scientists working in a particular scientific field.

CONCLUSION

Mr. Chairman, the request for the Division of Biologics Standards is $4,992,000, as compared with $4,817,000 available in 1964. The increase will provide for higher pay costs, and full-year cost of positions new in 1964. It will also provide for broadening the surveillance of clinical studies for new investigational biological products, strengthening the reference standards program, and additional staff for the legal office.

STATEMENT BY DIRECTOR, DIVISION OF BIOLOGICS STANDARDS, PUBLIC HEALTH SERVICE, ON BIOLOGICS STANDARDS

Mr. Chairman and members of the committee, this statement is made on behalf of the Division of Biologics Standards, to tell you what we are doing to carry out our responsibilities in the control of biological products used for the prevention and cure of diseases in man.

FUNCTION OF THE DIVISION

The Division's primary function is to administer those provisions of the Public Health Service Act pertaining to the safety, purity, and potency of biological products. The latter include the bacterial, viral, and rickettsial vaccines; antitoxins; therapeutic serums; human blood and blood derivatives; antivenins; venoms; and allergenic extracts. Many of these products are derived principally from pathogenic or potentially pathogenic micro-organisms, and their preparation requires careful control.

Experience has shown that such control can be accomplished most effectively within the context of an active research program. Thus, the programs of the Division are product-oriented; their scope, direction, and intensity are dictated by the need to provide essential information for the development of requirements and regulations for new products, as well as for the continuous improvement of tests to insure the safety, purity, and potency of existing ones.

IMPLEMENTATION OF FUNCTION

Control measures are based on a system of licensure. Following determination by the Division that the prescribed standards for safety, purity, and potency have been met, licenses for the manufacturing establishment and for the product are issued by the Secretary of the Department of Health, Education, and Welfare. The standards prescribed by the Division for biological products are set forth in regulations for their production and testing which are continually reviewed for adequacy by Division scientists. As scientific knowledge advances, revisions may be made.

Determination of eligibility for licensing of establishments and of biological products is a major part of the Division's program. Prior to licensing, the manufacturer's physical facilities must be inspected, his operating procedures observed, qualifications of his scientific and professional personnel reviewed, all data submitted with his application carefully evaluated, and representative samples of his product tested in the Division's laboratories. As of December 1, 1963, 204 establishment licenses and 1,320 product licenses were in effect, the latter covering 297 specific products.

Once a product is licensed, continuing surveillance is maintained by periodic inspection of the manufacturer's facilities and production methods, review of records of production and testing, and by the testing of representative samples of products in the Division's laboratories.

From December 1, 1962, through November 30, 1963, a total of 7,280 control tests were carried out in Division laboratories to insure the safety, potency, and purity of licensed biological products. The results of these tests served as a basis for the release of the more than 5,000 lots of products submitted by manufacturers during this period. Testing requires the skills of trained professional personnel to carry out the variety of procedures that are involved, ranging from relatively simple sterility tests to complex and costly potency determinations and safety tests.

Since most biological products cannot be standardized by chemical or physical means, their strength or potency must be tested in relation to established standard or reference preparations. In order to establish uniformity of potency of these products, the Division provides manufacturers and others engaged in biologics, standardization with these standard or reference preparations. Their development is dependent on advanced knowledge in a number of fields, including immunology, biology, virology, biochemistry, and medicine. Important problems in this work are the improvement of methods of preserving and storing, such as freezing and drying, so that potency is maintained; selection or development of preparations which yield clear-cut endpoints in the control testing performed by all manufacturers; and correlation, where possible, with standards established in other countries or with international standards.

This year, the Division distributed a total of 5,952 standard or reference preparations to commercial establishments, health departments, universities, and research organizations. Included were 378 antitoxins, 2,761 serums, 931 vaccines, 298 toxins, and 1,584 bacterial cultures.

Research to provide basic data on the properties of existing reference preparations, as well as new ones, is being carried out, and a program designed to maintain continuing evaluation of the stability of each preparation is in effect.

As in previous years, the Division has found it necessary to devote time and effort to problems raised by old established biological products such as yellow fever vaccine, smallpox vaccine, and typhus vaccine, emphasizing once again the need for continuing programs in areas which may have lost their glamour as subjects for contemporary research.

The prosecution of enforcement activities in connection with possible infringement of the law and regulations relating to biological products has continued. The Division cooperated on a continuing basis with the Food and Drug Administration in the field investigations of "Krebiozen" designed to secure information on the production, distribution, composition, and possible effectiveness of this preparation.

Field investigations concerning possible violations in the interstate shipment of human blood have been continued by the Division in cooperation with the Department of Justice and local health authorities.

For many reasons the Division has attempted to keep itself informed of the results of clinical and laboratory studies of biological products in the developmental stages prior to the initiation of any application for a license. In line with current interest in the nature and quality of clinical studies of investigative new drugs and their relation to safety, the Division now administers a program for monitoring clinical investigations of new biological products still in process of development and evaluation, thereby formalizing activities of this kind which have been conducted in the past.

The scope and variety of the research program necessary to support the basic control function of the Division is illustrated by the following examples of current interest and concern. These programs are of considerable value, not only because of the practical control application to which they give rise, but because of their contribution to the entire field of research and practice in the prevention and treatment of infectious diseases.

MEASLES VACCINES

Since November 1961, the Division has conducted a series of clinical studies in the Republic of Upper Volta, West Africa, using live measles vaccine. In this area, measles is exceedingly severe and is reported to be responsible for more deaths among children than any other disease. It has been estimated that measles with its complications is responsible for the death of 25 percent of the children infected during the annual epidemics in certain areas of West Africa. The first project was confined to a relatively small number of children who could be followed by observation and by laboratory tests. This established that despite their many health problems, Volta children respond to live measles vaccine in essentially the same manner as do American children. This project was also a dramatic field demonstration of the utility of the jet injector method of inoculation under a variety of conditions. This involves the jet injector "gun" which was developed in this country, and accomplishes the injection of a vaccine or other material using a controlled, fine, high-pressure jet for entry through the skin. The method dispenses with the hypodermic needle and is suitable for vaccinating large numbers of people in a short time.

Based upon the results of this study, both with regard to the evidence of protection against measles and the acceptance by the population of the "jet" method of inoculation, the Upper Volta Health Ministry urged the Division to continue with these studies. A program was worked out in cooperation with the Agency for International Development. This included attempts to demonstrate whether measles could be controlled in a discrete geographical area and to determine the feasibility of combined vaccination with measles vaccine, smallpox vaccine, and yellow fever vaccine.

Since measles is a seasonal disease, the question of success in controlling the occurrence of the disease can only be determined by the collection of epidemiological information, which is still being assembled. However, the studies did reveal that (1) combinations of live measles, smallpox, and yellow fever (17–D strain) vaccines can be safely and effectively jet inoculated into susceptible infants (an observation which will, of course, require more extensive study, but which could have considerable public health value in the control of these diseases in many countries); and (2) as determined by laboratory examinations of blood samples for measles antibodies, the live measles vaccine is fully effective for infants over 8 or 9 months old. It may be employed in still younger children but with a predictable reduction in efficacy because of the interfering effect of residual antibodies carried over from the mother.

INFLUENZA VACCINE

As far as we know, there is only one virus responsible for measles and this same virus causes the disease year after year. This is not true of influenza. A number of distinct types of virus are recognized as causing this disease, and even among these types the virus has a tendency to change its characteristics from time to time. An excellent example of this was the appearance in 1957 of a new influenza virus strain which was so different in its properties that when this became known it was immediately clear that existing influenza vaccines would not protect against it. This virus came to be known as the Asian strain and was later designated as a new type—A_2.

The Division, drawing its information and material from many laboratories in the United States and abroad, as well as from its own programs, keeps a continuing watch on the characteristics of any new influenza virus strain in order to determine whether the strain representation in the vaccine should be changed.

Since 1957, various strains of influenza viruses have been responsible for outbreaks of influenza but no significant changes in properties were noted until the winter of 1962–63. It was apparent that virus strains causing isolated outbreaks of influenza in Europe, the Far East, and New Zealand in 1962, and widespread influenze in Eastern and Central United States in the winter of 1962–63 were members of a relatively homogenous group of viruses within the influenza A_2 family which had undergone antigenic shifts of varying degree away from the prototype Asian strain responsible for the influenza pandemic of 1957. The vaccines available at this time contained the A_2 strain used since 1957.

Within months of the recovery of these contemporary viruses, the difference in antigenic composition between them and the prototype virus was demonstrated. A trial lot of vaccine containing a representative current strain of this variant A_2 influenza virus was prepared and found to elicit a satisfactory response in man as determined by laboratory findings. These studies were completed in time to incorporate a satisfactory contemporary strain of influenza A_2 virus into the polyvalent vaccine manufactured for commercial use in the United States during the 1963–64 influenza season.

Because of this propensity for change on the part of influenza viruses and because of the time involved in the study of a new strain, its adaption to manufacture, and the leadtime required for the manufacture of a new vaccine, situations are bound to arise in which the vaccine in use during a given season, i.e., administered in advance of the appearance of influenza, may be of less than optimal composition despite continuous alertness to the significance of new virus variants as they appear.

HEPATITIS

The contamination of blood products with the agent of homologous serum hepatitis constitutes one of the serious problems in medicine. Efforts of many laboratories throughout the world to transmit the agent of viral hepatitis, as well as the agent of infectious hepatitis, in tissue culture systems and laboratory animals have been unsuccessul.

Many physical, chemical and biological treatments have been attempted in order to educe a satisfactory technique for virus isolation from serum specimens having a high probability of containing one or another of the human hepatitis viruses. To date, all attempts have been unsuccessful. Some workers have made claims, but as yet none of them have been confirmed.

In 1961, a Division investigator recovered a virus in rabbit kidney tissue cultures inoculated with material known to contain the agent of homologous serum hepatitis. The agency, referred to as A–1, has been obtained from this source material only on one occasion, despite numerous attempts to reisolate it. Moreover, it has not been recovered from other materials known to have caused hepatitis in man. This A–1 agent is of considerable interest because it is neutralized by some serums from patients who have recovered from heptatitis. It propagates readily in a number of tissue culture systems including monkey, rabbit, chick, and human cells. Moreover, it produces readily observable cell changes in all of these cultures except in primary monkey kidney cell. It has failed to cause disease or any discernible changes in mice, guinea pigs, rabbits, embryonated eggs, rhesus monkeys, suckling mice, or suckling hamsters inoculated by various routes.

During the past year, attempts were made to further investigate the range of possible animal susceptibility to infection with the A–1 virus. Following inoculation with A–1 virus, chimpanzees, dogs, and cats are being closely observed for signs of disease.

PERTUSSIS VACCINE

The investigation last year of the instability of pertussis vaccine (used in the prophylaxis of whooping cough) when combined with poliomyelitis vaccine indicated that poliomyelitis vaccine per se does not affect the potency of the pertussis component of multiple vaccine preparations. It appears that the bacterial preservative used may contribute to the deterioration of potency. Studies are in progress to find a more rapid method to detect loss in potency during storage than the mouse potency test currently used. Additional studies have been undertaken to determine the stability of the pertussis component of new quadruple vaccines under varying storage conditions which simulate those encountered during distribution and clinical use.

ALLERGENIC PRODUCTS

Poison ivy.—Work on poison ivy extracts is continuing. In a collaborative clinical study it was found that the skin reactivity to pentadecylcatechol, once considered to be the active principle of poison ivy, was much less active than poison ivy extract. Work on relation of human skin sensitivity to the guinea pig assay, and on the presence of skin-reactive components other than catechols is being continued.

Tuberculins.—Continuation of studies on specificity of tuberculins has led to the discovery that the characteristic skin reactivity of tuberculin is associated with certain components. Progress in this work shows promise for the isolation of specific tuberculins. Use of such preparations would result in more meaningful epidemiological surveys for mycobacterial infections, a better understanding of the chemical and immunological nature of tuberculin-active components, and improved specifications for the manufacture of tuberculins.

CHOLERA VACCINES

The appearance of epidemic cholera in southeastern Asia in 1961 and its continued spread in areas of the Far East since then has stimulated worldwide interest in this disease which for many years was largely confined to the Bay of Bengal area where it is endemic.

The biochemical and antigenic differences between the El Tor vibrio of the current disease and the vibrios of classic cholera led some investigators to doubt the value of cholera vaccine for mass immunization against outbreaks of the El Tor infection. However, in studies of the El Tor organisms isolated during the 1961 outbreak it was shown that vaccines produced from the classic cholera vibrio strain, although varying somewhat in potency, gave the same degree of protection against both infectious agents when tested in laboratory mice. It remains to be definitely proven in adequately controlled field trials just how effective any cholera vaccine is in the prevention of cholera in man.

This year, Division investigators have found that the hemolytic property of El Tor organisms isolated in more recent outbreaks is much weaker than in the organisms isolated during the 1961 outbreak; in some instances this property is not demonstrable at all. The possible relationship of this change in character to the efficacy of the vaccines is currently under study.

The toxicity of cholera vaccine is also under study. In a recent pilot field trial of cholera vaccines, severe delayed reactions to a vaccine which appeared to have met all test requirements were observed. Information gained from these studies will lead to revisions of requirements for potency and safety of cholera vaccines.

TETANUS TOXOIDS

Because of its concern with the potency of toxoids and its ability to perform antibody determinations for tetanus antitoxin, the Division has been cooperating with public health authorities in the territory of Papua and New Guinea who are endeavoring to control neonatal tetanus which is a serious problem among the natives of that region.

The first phase of the collaborative study is nearing completion. Pregnant native women were immunized with five toxoid preparations. The antitoxin responses were determined at periodic intervals until delivery, and in some instances up to 1 year after the initial toxoid injection. It was shown that good antitoxin response can be obtained with a single dose of an oil adjuvant toxoid preparation, and that the antibody content may continue to rise for 6 months or longer after injection. No untoward reactions were observed. Apart from the valuable information derived from these studies as to the potency of tetanus toxoid preparations, which will be of assistance in any revision of the potency requirements, the demonstration of tetanus immunity following a single dose of toxoid would be of great value in immunization programs for hard-to-reach population groups.

BIOCHEMICAL STUDIES

The biochemical and biophysical aspects of virology, while providing some spectacular advances in fundamental virology, comprise an area from which many new discoveries of more practical importance in the prevention and control of infectious diseases are emerging. A number of biochemical studies carried out in the Division attest to the value of such work in relation to biologic products.

In a study of poliovirus, it was found that in the presence of the dye, proflavine, the virus becomes sensitive to light. Proflavine itself does not kill the virus but if such a sensitized virus is subsequently exposed to ordinary light, it is killed. This phenomenon is being studied in a variety of ways. For instance, if monkey kidney cells are inoculated with this virus and then irradiated with light, essentially all of the virus outside the cells is destroyed; however, many of the cells have been infected and will produce poliovirus when incubated at 37° C. A potential use of this application is the development and isolation of virus mutants that will become adapted to growth on cells which do not normally support their growth, a factor of some importance in the development of vaccines.

In another study, preliminary experiments to estimate the degree of sensitivity of measles virus to light have been conducted. The experiments indicate that exposure of live measles vaccine to bright sunlight for 5 minutes destroys more than 90 percent of the virus. This observation is of obvious importance for the proper packaging and handling of the vaccine.

TYPHUS VACCINE

The current typhus vaccine, which has been in use for over 20 years, is prepared by inactivating the typhus micro-organisms with formaldehyde. A live vaccine prepared from the attenuated E strain has been studied experimentally for a number of years by various investigators and may have some advantages.

Studies have been conducted in the Division to develop procedures applicable to the production and testing of stable, high potency, live attenuated typhus vaccine. A lot of freeze-dried vaccine has been tested for stability at various temperatures. The material remained stable after storage for 43 weeks at −20° C. Plans are being made to field test this vaccine in cooperation with other investigators when a suitable opportunity presents itself.

BLOOD PRODUCTS

Broad-based, comprehensive research directed toward the improvement of testing procedures for the control of biological products derived from human blood are being continued. These studies include research on freezing, storage at various low temperatures, thawing, and drying of the elements of whole blood which have therapeutic application, and the protein fractions of plasma.

There continues to be a growing interest in the components of the blood coagulation system. Techniques of fractional precipitation and column chromatography have been utilized by the Division in the characterization and purification of coagulation components, including the fibrinolytic system. Test systems for estimating purity of coagulation components are being investigated, and an evaluation is being made of assay techniques used in the coagulation field in order to determine the feasibility and usefulness of stockpiling coagulation reference products manufactured by present methods.

The increasing use of plastic containers for blood products has emphasized the importance of the Division's testing program of liquid plasma stored at 30° to 32° C. in plastic and glass containers. At regular intervals the samples are tested for loss of moisture and sterility. The stability of the samples is determined by ultracentrifugal electrophoretic, serologic, and immunochemical determinations.

In addition to these investigations, information will be developed from animal studies concerning the possible presence and significance of substances in plasma derived from the plastic containers.

There is some evidence that the so-called formed elements—i.e., red cells, white cells, and other discrete components of blood—can be separated in a completely closed system by use of high-intensity magnetic fields. A number of methods of accomplishing this separation using special centrifuges have been studied in the past and one such system has been used with good success by the National Cancer Institute.

The design and operation of equipment to separate red cells, platelets, and plasma by magnetoelectrophoresis is being investigated by the Division, and extension of research under contract is planned. If the system is successful, it will have the advantage of absence of moving parts within a truly closed system.

PROGRAM PLANS

Recently adopted Food and Drug Administration regulations require the monitoring of clinical trials of all investigational drugs. The Division must therefore maintain surveillance of all such studies being conducted on biological materials. With the adoption of these regulations, a unit within the Division was established to devote full time to this task. This group, which is to expand in 1965, will also collect and analyze data obtained from the clinical trials to assist the Division in the drafting of additional standards for new products prior to licensing.

The growth in the number and complexity of biological products emphasizes the need for more regulations and standards. In order to give maximum assistance to the investigators in the detailed legal and technical preparation of these regulations, an additional legal assistant is proposed.

The complex nature of the physical reference preparations, particularly those of viral origin, requires extensive testing to determine stability, optimal conditions of packaging and storage, and the precise results to be expected when they are used in the manner prescribed. To successfully meet these ever-increasing demands, the reference standards program will be strengthened.

These additional positions will require $75,000 of the increase proposed for 1965. The balance includes $15,000 for annualization of positions new in 1964, and $89,000 for costs of the pay increases which will be partially offset by a decrease of $4,000 for one less day of pay in 1965.

SUMMARY OF BUDGET

Mr. Denton. The appropriation for 1964, including the pending deficiency request, is $4,817,000 and the request for 1965 is $4,992,000, an increase of $175,000 and five positions. Is that right?

Dr. Murray. That is correct, sir.

POSITIONS FOR INVESTIGATIONAL DRUG WORK

Mr. Denton. Why do you need these five positions?

Dr. Murray. We have this year an extension of our responsibilities in the area of investigational new drugs. This is parallel with the program that the Food and Drug Administration has for investigational drugs in general. This applies to biological products and in that area a request has been made for $28,000. That will be two positions.

Mr. Denton. I am not sure I understand "biologic." That is something made from an animal product; is that it?

Dr. Murray. No. The word "biological" of course means "of live origin," but in this particular connotation, the word "biological" means "a group of medicinal preparations" which are derived from pathogenic micro-organisms, from animal serum, which we would broadly regard as vaccines and serums and analagous products.

Mr. DENTON. You investigate those, rather than the Pure Food and Drug?

Dr. MURRAY. That is correct.

Mr. DENTON. Do you have an agreement with them?

Dr. MURRAY. We have a law which requires us to do this; yes.

Mr. DENTON. And these five positions are needed where? State that again.

LEGAL ASSISTANCE

Dr. MURRAY. What we need are a total of five positions. One is to increase our legal capability. This is the legal assistance, because we have in connection with these requirements——

Mr. DENTON. Why doesn't the Solicitor take care of the legal questions?

Dr. MURRAY. As far as policy is concerned, sir, but we do need people who are skilled in legal thought so that we can draft regulations for further approval.

Mr. DENTON. Dr. Shannon, we do not have any lawyers any place else in these Institutes, do we?

Dr. SHANNON. No, sir. As a matter of fact, he is not even employed under the title. We are not allowed to employ a lawyer as a lawyer.

Dr. MURRAY. The lawyers are in the General Counsel's office.

Mr. DENTON. But this man is a lawyer.

Dr. SHANNON. I think one of the things Dr. Murray ought to point out is our ability to deal with the General Counsel and make the most use of that activity there in part depends upon our having an understanding of how the legal mind works.

Mr. DENTON. I would like to see lawyers have employment, but we have them everywhere. We have them in the Justice Department, and each agency has a solicitor's office and we are getting down to the divisions now.

Dr. MURRAY. No. We have one person with legal training in our Division at the present time who has the responsibility of working with the scientists in the Division in the promulgation of regulations which are then submitted to the General Counsel's office for final working over and adoption.

Mr. DENTON. Tell me what the rest, the other four will do?

Dr. MURRAY. As I mentioned there will be an increase of two in the area of surveillance of clinical studies; and this is to implement the responsibilities we have for biological products which are under course of clinical investigation.

For instance, I can cite at the present time, we have under active consideration over 70 such products, and this requires a great deal of professional attention. This is why we are asking for that.

Mr. DENTON. You have two more. What are they for?

Dr. MURRAY. Those are to expand our capabilities in the area of standard preparations. These are preparations which are sent out to the manufacturers of biological products so that with properly designed tests, they can match the strength, or the potency, of their products against these preparations.

Mr. DENTON. You don't have people working for you now that do that?

Dr. MURRAY. We do have people working for us now who are doing this at the present time. However, the increasing number of new products that are coming along, particularly in the area of viral vaccines, new vaccines against virus diseases, requires us to do a great deal of investigative and preventive work in connection with the development of these standards.

Mr. DENTON. These five—how much of this increase goes for their salary?

Dr. MURRAY. A total of $42,000.

Mr. DENTON. What, in round numbers, does the other $133,000 go for? What is the other $133,000 increase for?

Dr. MURRAY. The rest of the money is largely in the adjustment of pay increases and annualization of costs initiated during the previous year. That comes to $100,000.

Mr. DENTON. There is still $33,000.

Dr. MURRAY. That is for other objects: Associated expenses, that result from merely having a person with us, such as paying for any necessary travel, supplies, and so forth, that would be consumed the execution of the duties.

PLANS FOR NEW BUILDING

Mr. DENTON. Are all your employees in the new building?

Dr. MURRAY. Except for some that are in animal buildings, which are close by.

Mr. DENTON. I believe it was last year or the year before, that the building was brand new. You just got in the building, and it was not large enough.

Dr. MURRAY. That is correct, sir. Planning for the present building that we are in was initiated somewhere around about 1956, at a time when there was no full realization as to the size of the program that would be needed to mount the responsibilities in this area following the development of all of the newer products. By the time the building was completed in 1960, it was very obvious that although it had looked pretty adequate in 1956, this was an inadequate size, and in consequence, we have almost completed the design of the new addition, with funds that were appropriated last year.

Mr. DENTON. How are you coming along with that addition?

Dr. MURRAY. The design is almost completed.

Mr. DENTON. Is there anything else you would like to say?

Dr. MURRAY. If there are any questions, I would be pleased to answer them.

I don't feel there is anything more that I can say, other than what is in the statement, sir.

Mr. DENTON. I think that is all. We shall adjourn until 10 o'clock tomorrow morning.

Wednesday, February 26, 1964.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

WITNESSES

DR. ROBERT A. ALDRICH, DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. DONALD HARTING, ASSISTANT DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

CALVIN B. BALDWIN, Jr., EXECUTIVE OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

GERALD ATCHISON, BUDGET OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTE OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
11 Personnel compensation:			
Permanent positions	----------	743	931
Positions other than permanent	----------	28	30
Other personnel compensation	----------	23	20
Total personnel compensation	----------	794	981
12 Personnel benefits	----------	84	104
21 Travel and transportation of persons	----------	109	146
22 Transportation of things	----------	8	8
23 Rent, communications, and utilities	----------	3	4
24 Printing and reproduction	----------	6	10
25 Other services	----------	189	220
Payment to National Institutes of Health management fund	----------	108	146
26 Supplies and materials	----------	33	86
31 Equipment	----------	73	108
41 Grants, subsidies, and contributions	----------	32,162	41,362
Subtotal	----------	33,569	43,175
Deduct quarters and subsistence charges	----------	6	6
Total obligations	----------	33,563	43,169

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	----------	139	159
Full-time equivalent of other positions	----------	3	3
Average number of all employees	----------	95	124
Employees in permanent positions, end of year	----------	122	142
Employees in other positions, end of year	----------	10	10
Average GS grade	----------	8.2	8.4
Average GS salary	----------	$7,743	$7,967

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research		25,656	34,718
(*b*) Fellowships		2,364	2,364
(*c*) Training		4,142	4,280
Total, grants		32,162	41,362
2. Direct operations:			
(*a*) Research		120	291
(*b*) Collaborative studies		427	437
(*c*) Review and approval of grants		431	482
(*d*) Program direction		423	597
Total, direct operations		1,401	1,807
Total obligations		33,563	43,169
Financing: Unobligated balance lapsing		437	
New obligational authority		34,000	43,169
New obligational authority:			
Appropriation			43,169
Transferred from (76 Stat. 1072–1074)—			
"General research and services, National Institutes of Health"		9,646	
"National Cancer Institute"		1,146	
"National Institute of Mental Health"		6,914	
"National Heart Institute"		4,981	
"National Institute of Dental Research"		523	
"National Institute of Arthritis and Metabolic Diseases"		5,980	
"National Institute of Allergy and Infectious Diseases"		1,606	
"National Institute of Neurological Diseases and Blindness"		3,204	
Appropriation (adjusted)		34,000	43,169

Mr. FOGARTY. The committee will come to order.

We have before us this morning the National Institute of Child Health and Human Development.

GENERAL STATEMENT

Mr. FOGARTY. Dr. Aldrich, do you have a statement for the committee?

Dr. ALDRICH. Mr. Chairman, I have a statement which is about 20 pages long, and I have made a summary of it.

Mr. FOGARTY. All right. We shall put the full statement in the record. You may summarize it.

(Information to be furnished follows:)

Mr. Chairman and members of the committee, it is with particular pleasure that I appear before you today to describe the progress made by the National Institute of Child Health and Human Development during its first year. When I came before this committee last year it was to speak of concepts and planning for the future. Today, it is satisfying to be able to report some solid accomplishments and generally good progress toward the objectives stated before this committee.

Our first task was to organize the Institute in a manner which would prove most efficient and effective in discharging its unique responsibilities. The general concept underlying this Institute differs substantially from the categorical institutes and, therefore, required special consideration of administrative and staffing structure.

The Institute's primary focus is on the process of human development throughout the lifespan, or, time applied to biology. We are studying the living process—from the first spark of life, to birth, through childhood into maturity, and the changes connected with aging and senescence. Concomittantly, the institute is concerning itself with complex health problems that are related to the developmental process.

Typical examples of such developmental disorders are: mental retardation, congenital malformations, and prematurity. Research and training directed toward understanding human development must draw from virtually all disciplines ordinarily considered to fall within the fields of the biologic, behavioral, and social-cultural sciences. It may be that we will witness in the years ahead a new integrative discipline emerging in our universities which could be called human development.

ORGANIZATION AND STAFFING

A special report has been submitted to the committee, as requested, on organization and staffing. This report portrays the administrative organization of the Institute, the pattern of staffing with professional and nonprofessional personnel, the membership of the first National Advisory Child Health and Human Development Council, and includes consideration of problems which we have encountered during this initial period.

Progress in staffing and organization has been quite successful under the circumstances but the recruitment of top level scientists for our most responsible positions is hampered by present salary ceilings. We are unable to compete economically with universities and research institutes for the personnel we want. On the other hand, there is evidence of great interest among leading scientists and, if the President's executive pay bill is enacted, we expect that the recruiting circumstances will improve.

TRANSFER OF GRANTS TO NICHD

The transfer of grants from other Institutes to NICHD is very nearly completed. Most of this task was accomplished during the summer months so that by mid-November 1963 the bulk of the transfers had been completed. At the present moment there remain a few additional items which are under negotiation. The large group of transferred grants was approved by the National Advisory Child Health and Human Development Council at its meeting in November. Subsequent transfers will be considered by the Council at its March 1964 meeting.

The transfer was accomplished by a thorough review of all the grants held by NIH. This large number of grants was reviewed three times by myself and the NICHD staff. Those grants deemed most relevant to the programs of this Institute were separated and rated according to the degree of relevance to specific program areas. Each successive review reduced the initial list substantially so that the third list was highly relevant to our program.

Many grants were relevant to both a categorical Institute and NICHD. Negotiation was conducted with the respective Institute Directors, so that guidelines could be established suitable for future use in assigning grant applications to the appropriate Institutes. At the end of calendar year 1963, the total amount of grants and awards transferred to NICHD from the categorical Institutes was $20,894,791.

A chart has been prepared which shows the distribution of this sum among research grants, training grants, awards, and fellowships, and this is further expanded to show how these are distributed among the NICHD eight principle program areas (chart I).

CHART I.—*Grants and awards transferred by program*

[In thousands]

Program area	Number	Research grants	Training grants	Fellowships	Total dollars	Percent
Reproductive biology	143	$2,112	$883	$270	$3,265	15.6
Perinatal biology	212	3,379	631	284	4,294	20.6
Growth and development	260	4,752	1,304	320	6,376	30.5
Adult development and senescence	54	2,480	165	80	2,725	13.0
Mental retardation	54	1,980	123	63	2,166	10.4
Congenital malformations	56	1,113	8	119	1,240	5.9
Developmental pharmacology	21	317	------	20	337	1.6
Human communications	35	422	------	70	492	2.4
Total	835	16.555	3,114	1,226	20,895	100.0

Inspection of this chart brings out some interesting facts about the amounts and types or research already being supported by the National Institutes of Health. Almost two-thirds of the transferred grants fell into three program areas: reproductive biology, perinatal biology, and growth and development. By comparison, support of aging research, mental retardation, congenital malformations, developmental pharmacology, and the field of human communications combined make up the other third. It is distressing to me to see the relatively small amount of research and research training activity in the field of developmental pharmacology. This area has been identified for vigorous stimulation in 1965.

Another table has been prepared which gives a breakdown of the transfer of grants and awards from the categorical institutes in dollar value (chart II)

CHART II.—*Grants and awards transferred by institute*

[In thousands]

Institute	Number	Research grants	Training grants	Fellowships	Total dollars	Percent
National Institute of General Medical Sciences	264	$6,442	$1,407	$405	$8,254	39.5
National Cancer Institute	17	283		34	317	1.5
National Heart Institute	87	1,154	355	192	1,701	8.1
National Institute of Allergy and Infectious Diseases	56	1,014		110	1,124	5.4
National Institute of Arthritis and Metabolic Diseases	111	1,780	1,123	104	3,007	14.4
National Institute of Dental Research	47	568		80	648	3.1
National Institute of Mental Health	201	3,747	229	276	4,252	20.4
National Institute of Neurological Diseases and Blindness	52	1,567		25	1,592	7.6
Total	835	16,555	3,114	1,226	20,895	100.0

The six centers for aging research formerly supported by the National Institute of General Medical Sciences, have now been transferred to this Institute. These are large multidisciplinary research projects involving substantial amounts of money and for this reason, the field of aging ranks high in the amount of funds transferred.

INITIAL SELECTION OF MAJOR PROGRAM AREAS

With the advice and assistance of consultants, the Institute staff has initially identified eight major program areas. These programs and the related health problems selected for emphasis are being approached utilizing the full range of methods for the support of research and training available to the Institute. The program areas are: reproductive biology, perinatal biology, growth and development, adult development and senescence (gerontology), mental retardation, congenital malformations, developmental pharmacology, and human communications.

Reproductive biology will seek through research to improve our understanding of the basic processes whereby life is propagated. Emphasis will be placed on parental factors and the early sequence of events leading from conception through embryonic formation.

Perinatal biology will concern itself with events occurring during the intrauterine period of life and their relations to infant survival and later development. Major emphasis will be put on understanding the biology and behavior of the pregnant mother.

Growth and development will primarily concern itself with the determinants of physical, intellectual, social, and behavioral development in the period from birth to full maturity. Major emphasis will be given to developmental health problems unique to infancy, childhood, and adolescence.

Adult development and senescence (gerontology) strives to understand the biological, behavioral, and social processes that account for the gradual decrease of vigor and fitness that is experienced by mature individuals in varying degrees with advancing years. This includes the study of the progressive changes that take place in a cell, a tissue, an organ system, a total individual, or a group of individuals with the passage of time. Special attention will be given to investigation of the middle years of adult life.

Mental retardation will mount a concerted research attack on the cause, prevention, diagnosis, amelioration, and treatment of this handicapping condition.

Congenital malformations will support research into the prenatal causes of structural defects which are present at birth. Emphasis will be placed on multiple organ system defects, their cause, prevention, and amelioration.

Developmental pharmacology will support research into the variation at the different stages of life of the effects of drugs and other therapeutic agents. Emphasis will be placed on studying the effects of these agents on various stages of mammalian prenatal life.

Human communications will study the complex mechanisms whereby human beings receive information from their environment and then are able to express themselves by means of coordinated interactions of organ systems. The normal development of this complex function resulting in language and speech will receive primary emphasis. Disorders of this complex process are major reasons for reduced learning capability.

RECRUITMENT OF PROGRAM DIRECTORS

Program recruitment efforts have been directed initially toward establishing strong administrative staffs in the Office of the Director and extramural grants management. We are searching the Nation for outstanding scientists who can provide the desired scientific leadership in our major program areas. It is a pleasure to report that three excellent men have joined the Institute staff in senior positions as a program director: Dr. Gerald D. LaVeck as Program Director in Mental Retardation, Dr. Dwain N. Walcher as Program Director in Growth and Development, and Dr. Norman F. Gerrie as Program Director in Human Communications. We have appointed acting program directors in each of the other fields, and we are negotiating with excellent scientists whom we wish to have head the Institute's other programs. We are in the late stages of negotiation for a director in the field of aging research and we are making good progress in recruitment for leadership in the field of reproductive biology and perinatal biology.

Our total staff now numbers approximately 80 individuals, of which 36 are scientific personnel.

PLANNING OBJECTIVES

One of the first objectives which I had in mind after accepting the position as Director of this Institute was the preparation of a sound plan for the orderly future growth and differentiation of this Institute. A major document is in preparation that describes the plans made by the Institute staff with the assistance of consultants. It is anticipated that a draft of this material will reach the Director, NIH, during 1964.

Aging

As indicated to you in my testimony last year, this Institute looks upon the process of aging as part of a chain in the sequence of life. The transfer of the six large multidisciplinary aging research grants to this Institute raises some important questions. There is a need to enlarge and improve research and training in gerontology, by the best mechanisms available to us. We have therefore initiated a thorough review of the programs of each of the aging research centers with participation of members of the National Advisory Child Health and Human Development Council and other consultants and advisors. The purpose of this review is to learn from those intimately involved in these programs how effective this approach to research and training has been.

As a second step, we will obtain the opinions and suggestions of medical and graduate school deans throughout the Nation. It is a significant fact that no medical schools presently have departments of gerontology. There seems to be growing interest in the problems of aging and we seek to learn how research and training can be implemented more extensively in the Nation's medical schools. Informal conversations with medical school deans and other university authorities leave the impression that a significant hurdle blocking the development of departments or divisions for aging is the lack of space and facilities.

In the late summer it was my privilege to travel to several centers in Europe for the express purpose of learning more about the organization of research and training in the field of aging. Attendance at the International Congress of Gerontology in Copenhagen provided an opportunity to meet with the largest group of authorities on aging in the world.

There was a clear expression among many of these leaders that aging should be considered to be a process which starts before childhood and that major contributions to aging research can be made by scientists working at any place in the time span of life. It was of interest that a number of the scientific papers presented at the Congress could equally well have been presented in a conference devoted to problems of children.

There was a consensus among these leaders that the greatest need in the field of aging today is for training of more scientists to carry on aging research. This is the main reason why we are turning to the medical schools to stimulate admintrative recognition of gerontology as a field of research and training so that we can broaden the base of opportunities for young men and women to enter this important area of medical science.

Growth and development

Growth and development is another major area to which we will devote attention during the remainder of 1964 and in 1965. A substantial body of knowledge has been created in the past regarding longitudinal growth of infants and children. None of these studies have followed the individual subjects into middle age or senescence. In some instances there has been intensive study of the infant and young child, but the program was discontinued after only a few years.

It seems feasible to search out the subjects of some of these inactive studies and continue the work, even though there is a gap of several years in the data. We are considering the cost and the needs for manpower to transfer this data to modern devices for data recording and retrieval. Substantial progress in knowledge of growth and development can be achieved by bringing the available information into readily useable form.

In connection with this, we plan to establish a national information center on growth and development, and we will initiate a search of the medical and biological literature back to the turn of the century to reference the world's literature on this subject. This will be accomplished through cooperation with the National Library of Medicine.

TECHNICAL COMMUNICATIONS

My thinking about the role of communications in this Institute has been influenced by the testimony of communications scientists and others before the Congress last year. We plan to make communications one of the primary operating areas in the Institute, using a wide variety of methods to obtain our goals.

Scientific information centers

In my testimony last year, Mr. Chairman, we proposed to establish a number of specialized information centers during 1964. These would be designed to provide national focal points for informational and consultant services related to research in reproductive biology, maternal health, child health, mental retardation, and aging. Since one of the first duties of each program director is to organize the scientific information impinging on his field, these information centers have a very high priority.

We added to our staff in January 1964, Dr. Charles L. Bernier, who is Chief of the Scientific Information Centers program. Dr. Bernier and the Institute staff have met with the new Director of the National Library of Medicine, Dr. Martin Cummings, and his staff, in order to coordinate our efforts. The NICHD Scientific Information Centers will take advantage of the recently operational MEDLARS program which should advance our informational work considerably.

However, it is quite possible that developing these centers will require not only the fullest utilization of present resources but also the development and construction of specialized information centers in university settings. A few universities which have particular strengths in the major program areas of this Institute have already indicated an interest in cooperating with us in establishing these centers.

Interdisciplinary conferences

The interdisciplinary conferences program was initiated in 1964. Three have been scheduled and carried out and the results of the proceedings are being prepared for publication. The first concerned itself with the unexplained causes of sudden death among infants. Two additional closely related conferences were held in December 1963 on the basic causes of prematurity, and the nature of hyaline membrane disease (respiratory distress syndrome of the newborn). Each of these conferences brought together approximately 30 of the world's leading scientists illustrating how this Institute can quickly assemble the full range of present-day knowledge on matters of interest to child health and human development. This series of conferences is continuing during 1964 and will be expanded and broadened in subject area during 1965. We plan to present conferences this year on aging research, reproduction, and the effects of chemicals and drugs in the prenatal period of life. We have assisted and participated in support of conferences and other informational activities related to mental retardation during 1964 and we hope to expand this program in 1965. The proceedings of these conferences will be printed and made available to the scientific community.

NATIONAL ADVISORY CHILD HEALTH AND HUMAN DEVELOPMENT COUNCIL

The first regular meeting of the National Advisory Child Health and Human Development Council was held in November 1963. New research and training grants were recommended for approval at this meeting. The council acted on the transfer of grants from other Institutes and considered major policy matters.

Special program planning committee

The Council recommended the appointment of a Special Program Planning Committee whose function would be to assist the Institute staff and the Council in the further definition of program objectives and scope. This action was advised in view of the wide range of responsibilities of NICHD. Recommendations of this Committee will be submitted to the National Advisory Child Health and Human Development Council for their consideration. I believe that this technique will advance the rate of program development.

Training committee

A Training Committee was appointed by the National Institute of Child Health and Human Development and was approved by the Council. Members of this Committee, whose professional backgrounds reflect the various research interests of this Institute, meet at least three times a year to review pending applications for training grants. The Committee in conjunction with the Advisory Council also serves as an advisory body periodically reviewing training needs related to child health and human development.

A committee to review research career awards and research career development awards is being selected; at present these applications are being reviewed by the NICHD Training Committee.

Developmental scientist training program

Of interest was the recommended approval of an experimental training grant to prepare young scientists for careers in research in human development.

The developmental scientist training program is designed to satisfy an urgent need to prepare investigators trained in greater depth and breadth in those basic sciences which underlie an understanding of growth and development. These investigators must be fully qualified as physicians. The program differs from other training activities in that it is focused on training medical scientists with human development as the principal focus. The program permits young men and women to enter the program at various stages in their medical training, thereby providing considerable flexibility.

Program-Project Committee

The Institute is establishing a Program-Project Committee to review the large multidisciplinary grants aimed at support of a program area. We plan to have this Committee operated by the Division of Research Grants with the members of the Committee chosen with approval of both the Division of Research Grants and the National Institute of Child Health and Human Development.

NEW MENTAL RETARDATION LEGISLATION—PUBLIC LAW 88–164

The legislation which provided for major new programs in mental retardation will undoubtedly become a historical milestone in medical research legislation. The National Institute of Child Health and Human Development has been working in close cooperation with the Division of Research Facilities and Resources of NIH so that the administration of the construction aspects of Public Law 88–164 assigned to NIH will be handled effectively. A subcommittee of the Council and the staff of the Institute has participated in drafting guidelines, policies and procedures, necessary for administering this act. The Institute has also been very active in program consultation with interested universities and it will use its present research and training grant authority to support the projects in training which will be carried out in these important new research centers.

Stimulation provided by the establishment of this Institute and the new legislation has already resulted in several major applications for construction of mental retardation research centers and we have evidence of intent to submit additional applications from other excellent universities in virtually every region of the United States.

RESEARCH GRANT SUPPORT

A significant increase is apparent in the number of applications for research support through the programs of this Institute. This is supported by an analysis of applications now awaiting action by the National Advisory Child Health and Human Development Council at its March 1964 meeting. I believe that this increase will continue to accelerate during the next several fiscal years and particularly during 1965. We expect to see a sharp increase in the numbers of research grant applications in reproductive biology, perinatal biology, mental retardation, growth and development, and aging. We are vigorously stimulating research activity in developmental pharmacology, congenital malformations and in the field of human communications.

Most of the increases in applications for support will come from those scientific fields where there already exists a pool of scientists who are properly trained to conduct research. We anticipate a lag phase before any substantial increase occurs in some areas because of lack of trained personnel.

TRAINING PROGRAMS

In 1964 NICHD has been stimulating applications for the support of training in all eight of its major program areas. We have endeavored to utilize fully the fellowship and awards programs as well as the training grant mechanism. There is an increase in the number of applications for research training in such subjects as human development, obstetrics, pediatrics, intellectual and behavioral development, and in teratology. We are encouraging cross disciplinary research training and specially combined training in obstetrics and pediatrics for those individuals who may consider entering careers of research and teaching in the problems of perinatal life. The broadly based human development research centers which were mentioned in testimony last year are being planned in some of our best universities and these will serve an important complementary role to the centers for research in mental retardation under Public Law 88–164. Each of these kinds of centers will be essential to the broadening of the total training effort by NICHD.

SPECIAL TRAINING PROBLEMS

NICHD planning activities and experience with the grants transfer have brought to light several special problems in training. Without adequate numbers of well-trained individuals it will be difficult to mount vigorous research in major program areas, particularly reproductive biology, developmental pharmacology, congenital malformation, and aging. I invite the committee's attention to the following:

Reproductive biology

There is reason to believe that expansion of training in the field of reproductive biology cannot be accomplished as rapidly as desirable if we are limited to resources within the United States. It is desirable that carefully selected centers of research in this important field that are located outside the United States should be utilized during 1965 for the training of Americans who then wish to return to the United States to develop strong scientific programs of their own in our universities and colleges. The National Institute of Child Health and Human Development plans to explore this possibility fully during 1964 and, if feasible, implement this plan as soon as possible.

Since a high priority has been assigned to basic research in reproductive biology, we expect to initiate during 1964 some collaborative studies utilizing the excellent primate colony located in San Juan, P.R., and operated by the National Institute of Neurological Diseases and Blindness. Discussions with the Director of NINDB have resulted in plans for NICHD participation in Puerto Rico. It is mutually desirable that this effort be enlarged and intensified in 1965.

Developmental pharmacology

Developmental pharmacology is greatly in need of increased numbers of trained personnel. There are not enough pharmacologists in the Nation and, of these, relatively few have concerned themselves with the developmental aspects of drugs and other chemicals. We need to know much more about the effects of these materials on prenatal life, particularly those agents used during obstetrical labor and in the early stages of pregnancy. The National Institute of Child Health and Human Development proposes to undertake vigorous measures to stimulate additional training opportunities in developmental pharmacology.

Congenital malformations

There are a number of sites in the United States where research in embryology and teratology is being carried on. Many of these are located in colleges or undergraduate departments of universities. During the remainder of 1964 and in 1965 we will stimulate the establishment of programs of research and training into the causes of congenital malformations in medical schools where such programs do not presently exist or can be expanded. Vigorous efforts are required to reestablish embryology and teratology as major medical school subjects so that young men and women interested in medicine and biology will be attracted to careers of teaching and research in these important subjects.

Aging

The National Institute of Child Health and Human Development is taking steps in 1964 to stimulate medical schools to establish departments of gerontology. These plans will be continued during the remainder of 1964 and emphasized increasingly in 1965. The training of gerontologic scientists will be given a high priority by NICHD as these new departments are established.

SUMMARY

During 1964 the National Institute of Child Health and Human Development has continued to develop its organization and staffing plans. The grants transferred from the categorical institutes of NIH totaled $20,894,791. The Institute is reviewing its needs in a number of program areas, particularly the field of aging, with a view toward providing more effective support for research and training needs. Plans for 1964 include collaboration with NINDB in research utilizing the primate colony in Puerto Rico. This will permit expansion of research and training in reproductive biology during 1965.

For these activities, Mr. Chairman, we are submitting a request for $43,169,000. This compares with an appropriation of $34 million for 1964 which was derived from transfers from the other institutes of the National Institutes of Health. Of this amount, $437,000 was placed in administrative reserve, leaving an operational budget of $33,563,000 in 1964. The budget requested for 1965 represents a total increase of $9,606,000 over the 1964 operational budget. This increased amount is distributed by activity as follows:

Grants:	
Research	$9, 062, 000
Training	138, 000
Total grants	9, 200, 000
Direct operations:	
Research	171, 000
Collaborative studies	10, 000
Review and approval of grants	51, 000
Program direction	174, 000
Total direct operations	406, 000
Total program increases	9, 606, 000

Dr. ALDRICH. Mr. Chairman and members of the committee, it is with particular pleasure that I appear before you today to describe the progress made by the National Institute of Child Health and Human Development during its first year. When I came before this committee last year it was to speak of concepts and planning for the future. Today, it is satisfying to be able to report some solid accomplishments and generally good progress toward the objectives stated before this committee.

ORGANIZATION AND STAFFING

During 1964, the National Institute of Child Health and Human Development has continued to develop its organization and staffing plans. The grants transferred from the categorical Institutes of the National Institutes of Health totaled $20,894,791. The Institute is reviewing its needs for expanded research and training in a number of program areas, particularly the fields of mental retardation and aging, with a view toward providing the most effective support. We are vigorously stimulating research activity in developmental pharmacology, congenital malformations, and in the field of human communications.

Plans for 1964 include collaboration with the National Institute of Neurological Diseases and Blindness in research which would utilize the primate colony in Puerto Rico. This will permit expansion of research and training in reproductive biology during 1965.

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In the general and longer statement, I have included a sequence of the things which we have done during the first year, and I have developed in considerable detail certain features.

One point that I would like to expand on briefly is the pattern of organization and staffing of the new Institute.

We have had excellent advice from experienced administrative people in Government and outside of Government, which has led us to place maximum emphasis in our organization on the subject under study. In other words, we have emphasized the objectives that we are seeking to meet, and we have not overemphasized, in my opinion, the methods used.

We have also been very fortunate, I think, in our recruiting activities. We have already attracted to the Institute three of our permanent program directors. We were able to have Dr. Dwain N. Walcher, who had been a professor at the University of Indiana, come in to head up our growth and development program. He has been with us since the latter part of the summer.

In mental retardation we were fortunate to get the services of Dr. Gerald D. LaVeck, who came from the State health department in the State of Washington, and he is heading up the mental retardation program. He has already developed a highly qualified professional staff to help him.

We were fortunate also to obtain the services of Dr. Norman Gerrie, who is a dentist, with a wide background of experience in the PHS. We have been able to recruit him as program director for human communications.

We are at a very late stage of negotiations for our program director in the field of aging. We have already developed some staff in this field. And we have acting program directors in each of the Institute's other major programs.

TRANSFER OF GRANTS

I would like to also say that the transfer of grants from the categorial Institutes, as mentioned by Dr. Shannon yesterday, was negotiated directly between myself and the other Institute directors. These transfers were made on the basis of program content after we had studied the grants individually, determined their program content and their appropriateness and relevancy to the programs of the National Institute of Child Health and Human Development.

In the opening statement on page four you will find tabulated the program areas to which we are giving major emphasis, and the amounts of grants transferred from all of the other categorical Institutes.

In another table we have shown the amount of grants transferred from each of the categorical institutes. This table is correct up to the end of calendar year 1963.

SELECTION OF MAJOR PROGRAM AREAS

I would like to say one other thing, Mr. Chairman. In selecting our major programing areas we have identified eight that we think are prime targets. In an effort to focus our attention on the unknown, we have picked rather broad areas. We have felt that there is a great deal of research that needs to be done in several fields, and rather than become involved in some subjects which one might ordinarily think would be properly placed within this Institute, we have tried to select those areas in which there is limited knowledge and where we could make the maximum impact.

The areas of major program interest are reproductive biology, perinatal biology, growth and development, adult development and senescence, mental retardation, congenital malformations, developmental pharmacology, and human communications.

In my opening statement we have provided a definition of what these program areas cover.

I would, if I could, just take one more moment to identify in the structure of our Institute something which we feel is very necessary and a little bit unique. We are giving maximum emphasis to technical communications. We find that by combining interdisciplinary conferences with the establishment of scientific information centers, we can bring together total information about a program area. In this way we can better identify areas where there is limited knowledge and, I think, make the best use of the funds available for research.

In our dealings with university faculties we have been very pleased to see that this approach is appealing to them. We have entered into a number of discussions with leaders in research in the universities in our program areas and find that by working with them to assemble all of the knowledge in a given field, like prematurity, or hyaline membrane disease, when decisions are made about support of research or training of personnel, we are leading off from the best available knowledge, not only in this country but abroad.

So, with these comments, sir, I think I have covered the main highlights.

ADMINISTRATIVE RESERVE FOR 1964

Mr. FOGARTY. The Appropriation Act for 1964 authorizes the transfer to this new Institute of $34 million. The request for 1965 is $43,169,000.

Are those figures right?

Dr. ALDRICH. Yes.

Mr. FOGARTY. I see you have a reserve of $437,000.

Why is that?

Dr. ALDRICH. This is the amount that was placed in administrative reserve. It represented the best judgment, at the time, of funds that might not be obligated at the end of the fiscal year.

Mr. FOGARTY. When was that?

Dr. SHANNON. Late fall.

Mr. FOGARTY. What is your best judgment? Your best judgment now.

Dr. ALDRICH. I will have to answer you, sir, by saying that it is too early for me to be very definite. It is possible that we will have an unobligated balance in the vicinity of $5 million at the end of this year, but in my own personal judgment it may be substantially less than this.

The reasons for this are pretty straightforward.

The first reason is that the efforts of our program directors who came on board in the fall are just now beginning to result in a considerable increase in the number and size of grants that are coming in. Many of these grant applications are very imaginative and extremely interesting, and if these are processed and approved by the Council in this fiscal year, I think this might result in a substantial reduction in the unobligated balance.

A second consideration is related to the size of the staff that we had available during the summertime. We were limited in the number of visits we could make to explain the program of this institute to university faculties. These considerations will not be as significant next year.

RECRUITMENT FOR TOP POSITIONS

Mr. FOGARTY. You say on page 71 that—

> an intensive search has been conducted for outstanding scientists to provide leadership in major program areas.

You have done pretty well, have you not, in that so far?

Dr. ALDRICH. Yes.

Mr. FOGARTY. What are the remaining ones you are looking for now?

Dr. ALDRICH. Well, we are looking for a leader, a man to take over the program direction in reproduction. We have someone acting in this role now who happens to have a very good knowledge in the field, Dr. Gilbert Woodside, who was the provost of the University of Massachusetts. His field is closely related to reproductive biology and he has been giving us good guidance. A second man we are looking for is our program director in perinatal biology. We are very hopeful, sir, that we will be able to attract one of the outstanding obstetrical scientists in the country. There is great interest in this position and it means moving a senior scientist from a very good university into Government. I am very optimistic about filling this position between now and the summertime.

I mentioned that we had filled the growth and development post. We hope to have an answer on the adult development and senescence post within the next few weeks.

We have our Mental Retardation Director.

We are also negotiating now with a man to head up the program in congenital malformations, and if this goes as I hope it will, we should have him with us this summer, or, at the latest, by next fall.

In developmental pharmacology we have two leading candidates, one of whom was, as he put it, "thinking it over carefully," and we may have this program director available to us by summertime. We have filled the human communications post.

So that we have five positions to fill permanently, but we do have good people serving as acting directors, and talented junior staff members.

Mr. FOGARTY. Almost all of your requested increase is in research grants.

Dr. ALDRICH. Yes.

Mr. FOGARTY. This would enable you to support 1,077 research projects in 1965 compared with 758 this year.

HIGH PRIORITY FIELDS OF RESEARCH

Now, to what field of research are you giving particular emphasis?

Dr. ALDRICH. Well, sir, I cannot exactly arrange our program fields in their order of relative importance. I think I should just say it appears to us that the greatest limitations in research are probably in the fields of congenital malformations and developmental pharmacology. There is a crying need for more work in mental retardation at a very basic level. I would identify adult development and senescence as being another. I certainly would not want to leave reproductive biology out. I think this is a crucial field for basic research. So, you can see we have four or five specific areas of very high priority.

Mental Retardation

Mr. FOGARTY. All of these areas are important. In mental retardation, you are playing a large part. But Dr. Felix and Dr. Masland have activities aimed at the problems of the retarded in their Institutes, too.

Tell us what your program is, and tell us how it is different than the programs of the Mental Health Institute and the Neurological Institute, and whoever else is doing work in that field.

Dr. ALDRICH. All right. The three principal Institutes that are involved in mental retardation are the National Institute of Mental Health, the National Institute of Neurological Diseases and Blindness, and the Child Health and Development Institute.

We have within NIH a staff group which was established with representation from these three Institutes I mentioned, and also with representation from the Division of Research Facilities and Resources, because they have the administrative authority for the funds that are to go to construct the mental retardation research centers. So there are really four groups that are intimately involved here. This staff group is chaired by Dr. LaVeck, our program director on mental retardation, with representatives from each of the other parts of NIH that I mentioned. This group is a coordinating group, and we have found that it is very effective in dividing up the areas of responsibility within NIH. There is bound to be a certain amount of overlap between the interests of the Institutes. And this staff group has been very helpful in identifying the areas of overlap and the degree to which they overlap, so that we are not duplicating effort to any greater extent than is absolutely necessary.

Mr. FOGARTY. Why not confine yourself now to telling us what you are doing and what the Mental Health Institute is doing and what the Neurological Institute is doing?

Dr. ALDRICH. Yes. I would like to use an example of the relationship between the National Institute of Mental Health and the National Institute of Child Health and Human Development.

In the field of mental retardation, cultural deprivation is an important contributing cause, and may be the primary cause of mental retardation in a good many children. On the other hand, we are very much interested in and consider ourselves as having a primary interest in normal intellectual development and the normal learning process. Now, we feel that the National Institute of Mental Health should place its primary emphasis on disorders of learning rather than on normal learning, so they are obtaining leadership in the cultural deprivation area of mental retardation, whereas our emphasis is beginning to be on the learning process itself, whether it happens to be in a mentally retarded youngster or in a normal youngster. So there is a real division of labor.

LEARNING PROCESS

Mr. FOGARTY. What do you mean by "learning process?"

Dr. ALDRICH. Well, we are interested in how normal children learn.

Mr. FOGERTY. Learn what?

Dr. ALDRICH. Learn, for example, how to speak; learn to recognize objects and people. In other words, assimilate themselves into our society, whether it is in the family or in the town.

If you stop to think about it, an infant must learn a great deal from his parents and from his brothers and sisters simply by observation before he has learned to speak. What I call silent language. He then puts together the words or the sounds that he hears with the motions and actions he observes in his family group and learns that they have a relationship. Then he is able to speak and express these images with words; words that have meaning, so I think this gives you some idea of what the process of learning is in a young child.

Then, there are other aspects of learning such as reading. We know pretty well that, at least with a normal child, it is very difficult to get them to learn to read much before they are 5 years of age, and then something or other happens. We do not know what the "something or other" is but it happens around 5 or 6 years of age, when all of a sudden they are able to make these complex associations in their mind which we call reading.

Mr. LAIRD. What are you going to do when you find this out? What is this going to do for us?

Dr. ALDRICH. Well, I think if we can understand how an individual learns we may be able to help people to learn to read more quickly.

Mr. LAIRD. You mean he should start this learning process at an earlier age; is that it?

Dr. ALDRICH. Let me turn it around a little, Mr. Laird.

It is not so much whether I think they should start earlier. It seems to me that we may find it useful in our civilization to understand all of the links in the learning process. There may be parts of the learning process that have to be learned at a certain time in our life. If you are not exposed to learning something at the right time it is much more difficult for you to learn it later on. The old saw about "teaching old dogs new tricks" may well be true. We have to understand what the normal chain of learning is if we are going to use this information to help ourselves.

One of the biggest problems that faces schools, colleges, institutions of higher learning, and graduate schools, is the fact that really quite a lot of people do have trouble learning. It may be some part of learning. It may be that they have great difficulty recognizing words, or they may read very slowly instead of reading very rapidly as some of us do.

I think there is intrinsic value, to answer your question specifically, in understanding what the learning process is. I am not at all sure I can define in advance just exactly how this information would be used.

Mr. FOGARTY. What else are you doing in mental retardation?

Dr. ALDRICH. I thought I would go into this in a little more detail.

DIVISION OF RESEARCH ON MENTAL RETARDATION

In discussing mental retardation, I am including the other two Institutes and also keeping in mind what the Office of Education is doing in this field.

In our relationship to the National Institute of Neurological Diseases and Blindness, I think we have worked out a very good division of labor. Their focus, as it must be, is primarily on the nervous system. And our focus is primarily, for purposes of prevention of mental retardation, on the prenatal phases of life when a good deal of the things happen that result in mental retardation. We believe that by studying the formation of the embryo, by studying the growth and the development of function in the fetus prior to birth, that we can begin to understand what goes wrong, what happens to the embryo that may result in a malformation, or what may happen to the mother that interferes with the establishment of functions in the fetus before it is born.

So our approach is very broad. It is not limited to the nervous system at all. It involves studies of many different organs. It involves studies of everything, really, that affects the fetus.

I think we may be seeing a new medical discipline evolve which one might call fetal medicine. This discipline would concern itself with the health of the fetus prior to birth.

I think what I am trying to illustrate is the division of labor. We are looking at the embryo as a whole, the fetus as a whole, and the process of labor and the relationship that this unborn infant has to its mother. We are particularly interested in the things that happen to the mother that may be reflected in the development of the fetus.

Her illnesses; the medications that she takes, and so forth. So, I do not think that we are in any way getting into the Neurological Institute's primary field in this regard, although much of this research can be related to mental retardation.

Well, part of it is.

Mr. FOGARTY. Part——

Dr. ALDRICH. This is broader than just mental retardation, but this is our general approach, sir.

PERINATAL RESEARCH

Mr. FOGARTY. Is there any connection with this approach and the collaborative perinatal research program?

Dr. ALDRICH. The collaborative perinatal research project is, of course, of great interest to us, particularly some of the excellent results which are now beginning to come out of this study. We have established a very close liaison with Dr. Masland that has resulted in several meetings with him and some of his staff. He and I have talked a number of these things over. So, I feel we are extremely well informed on what they are doing and I think they are well informed about our program.

Mr. FOGARTY. What are you doing in perinatal research?

Dr. ALDRICH. Well, this is a topic I should expand on some.

Our real solid move in this direction began with the three conferences that we held in the fall of 1963. One was to try to establish the causes of a mysterious snydrome resulting in sudden death of infants. Another conference was on the factors which cause obstetrical labor to begin. This is a fundamental unknown, we do not really know what starts labor. The reason we are interested in this problem is that if you are going to have a premature infant, something has to start off labor, so the infant is born ahead of schedule, and is therefore subject to all the difficulties of prematurity. We brought together for that conference some 25 or 30 of the world's leading scientists in this field, not only from this country but from other nations. The transcript of this conference has just been received and we are now editing it for publication.

I dare say, sir, that this was one of the most significant exchanges of first class scientific data and scientific ideas that I have participated in. This has been verified by many of the people who were there, and we will move along the leads that came out of this conference as rapidly as possible.

The third conference which was also related to perinatal biology was centered on the way in which a newborn infant adapts itself to extrauterine life and begins to breathe. It is in these first few hours, really, the first 24 to 48 hours, that the hyaline membrane disease occurs.

We are not only interested in the fact that about some 45 or 50 percent of these youngsters who develop hyaline membrane disease may not live, but we are also interested in the fundamental physiology of this disturbance. We hope that we can solve this problem by following some of the excellent leads that came out of this conference.

I mentioned "Surfactin," which appears to be a substance elaborated by cells in the lungs. Perhaps this material can be prepared in pure form and may possibly, when subjected to clinical trials, be used in the treatment of hyaline membrane disease.

As you can see, these illustrations combine program planning and program action and I think this approach is effective.

RELATION TO ACTIVITIES OF OFFICE OF EDUCATION

Mr. Fogarty. Now, is there any duplication or overlap in what you are doing in mental retardation and what the Office of Education is doing? In some of their cooperative research programs, for instance.

Dr. Aldrich. I do not think there is overlapping, Mr. Chairman. We have discussed this with Commissioner Keppel on several occasions and he has expressed the view that they will center their efforts for the time being on applied research, the application of knowledge to the problems that are before them.

We have made it very clear that we consider our main effort to be in basic research in learning. So there is a clear division of labor, but a great common interest. We have very cordial relationships with the Office of Education.

MOTHERS SMOKING RELATED TO PREMATURE BIRTHS

Mr. Fogarty. I do not know whether you are the right person to ask, but a year or two ago it was stated by someone that excessive smoking by the mother causes premature births which, in turn, has some relationship to mental retardation.

Do the statistics still stand up?

Dr. Aldrich. There is a very good study that shows that the mothers who smoke to a high degree do have infants with smaller birth weight. The thing that is lacking is any evidence that that group of infants who were small presumably because their mothers smoke are less healthy than the infants who are heavier at birth.

Mr. Fogarty. I thought there was some information along that line.

Dr. Aldrich. I do not believe so. We have always thought, and this is a general feeling that people in pediatrics and obstetrics have, that the small infant is likely to have more troubles, especially if he is premature. But in this particular study that you have mentioned, I do not believe that they presented evidence that, just because they were small, they had any particular difficulties.

Mr. Lesinski. Mr. Chairman, last year we were acquainted with the fact that the women who smoked perhaps had more premature babies. Not "small babies," though.

Dr. Aldrich. These were small.

Mr. Lesinski, you have brought up an important point that we are working on. The definition of "prematurity" that is generally used today in our vital statistics and by most university centers is that the baby is premature if he weighs under 2,500 grams.

Mr. Fogarty. How many pounds is that?

Dr. Aldrich. About 5 pounds, 8 ounces.

Mr. Lesinski. In other words, prematurity is below 5 pounds 8 ounces.

Dr. Aldrich. Yes. This is a weight standard used in the United States and abroad right now. But we hope to define more precise physiological standards of prematurity. This is one of the things we will be working on.

Mr. Lesinski. Well, there is a difference between a full 9-month baby and a 7-month baby.

Dr. Aldrich. Right.

Mr. Lesinski. Or 8-month baby. Because he is not completely developed at 7 months.

Dr. Aldrich. Correct.

Mr. Lesinski. That is where you have problems. So why should you lump them altogether?

Dr. Aldrich. That is what we want to know, sir, what the difference is in physiological function of an infant who has only had 7 or 8 months of gestation and one who has had 9 months. There is a difference in weight, I certainly agree with you, but——

Mr. Fogarty. Do you know why excessive smoking causes this?

Dr. Aldrich. I do not know, sir.

Dr. Shannon. Mr. Chairman, one cannot conclude that it causes it, but there is an association. In other words, you may have common causes for two things. Causal relationship and association are two quite different things. At this point in time, all we can do is point out association without drawing any conclusion as to causation.

Mr. Fogarty. I think that is what Dr. Masland had in mind when he said last year: "Prematurity is more common in women who smoke." So it was not really pinned down.

I just wonder why, since excessive smoking over a period of time causes lung cancer and difficulty in people who have heart conditions and women who are pregnant, why we continue to subsidize tobacco production in this country?

That is moving out of your field, Doctor.

Mr. Michel. As a matter of fact we might be subsidizing the other side of it to find out how we can grow tobacco that will not do these things that the other research says are harmful.

CONGENITAL MALFORMATIONS

Mr. Fogarty. Now, in the field of congenital malformations, including such things as cleft palate—what are you doing in this area and how is it different from what the Dental Institute is doing?

Dr. Aldrich. Well, this is again an area that we have worked out by negotiation with the Director of the National Institute of Dental Research. What we are doing is this, we are looking at all congenital malformations. This is such a very broad problem that we felt it would be inconsistent to leave out a major, well-known malformation which has very important health ramifications just because it was under study by another Institute.

After talking to the Director of the Dental Institute we decided that the main objective was to broaden the amount of research that is conducted into the causes of cleft palate, and, collectively, to develop a lot more interest in this problem in the medical schools and in the graduate schools among those people who are interested in teratology and the experimental induction of malformations in animals.

We found from studying the NIH grants related to cleft palate that practically all of them—not all of them, but practically all of them were in dental schools. And since we had through our Institute a very good opportunity to work with those most interested in human development, the people in pediatrics, embryology, and obstetrics, we felt we could greatly broaden the base of research in cleft palates by bringing the dental schools, and the medical schools together to combine and coordinate their efforts in this important field.

This is our objective, sir; we have again defined our objective and split up the work, so that I think it is going to be very efficient.

EFFECT OF DIET ON HUMAN DEVELOPMENT

Mr. Fogarty. What are you doing on the effect of diet on human development?

Dr. Aldrich. So far, we have done mostly planning in this field. I can tell you a couple of things we have decided to undertake.

One is, we are going to go into what I call body composition in a pretty extensive manner. We want to identify the changes in, say, the embryo of fetus of the young child as compared to older individuals. This will be done on several kinds of animals including the use of monkeys as human counterparts. But even so, there can be some very good studies done on body composition of human beings with carefully tested scientific methods.

We are also going to work very closely with the Office of International Research at the NIH in making some studies of people who live in areas with chronic malnutrition.

Mr. Fogarty. With this budget, you are not going far.

Dr. Aldrich. Well, we are going to do the best we can. But we think that malnutrition is something that has not been stamped out in this country as well as in other nations, and that much of what we learn by collaborating, for example, with INCAP in Guatemala, we could apply in this country, too. Nutrition as a subject of interest does not occupy the center of the stage it had 25 or 30 years ago. But I think it is coming back and we intend to stimulate it very strongly.

Mr. Fogarty. Several years ago we had some outside witnesses come before the committee who were experts in the field of nutrition. I thought they made a pretty strong case that it was very important, but we never seemed to get off the ground with a really comprehensive study.

Dr. Aldrich. There is a renaissance, if I can use that word, in basic nutrition, which I think is a byproduct of the terrific advances in biochemistry that have taken place in the last 15 or 20 years.

ACTIVITIES RELATED TO AGING

Mr. Fogarty. What are you doing in the field of aging?

Dr. Aldrich. Dr. Harting is our "aging" expert.

Dr. Harting. I might pick up specifically your inquiry about nutrition, because one of the most interesting grants we have reviewed and extended the support for is being done by the Biochemical Research Foundation in Delaware, in which they are carrying 3,700 rats under very carefully controlled nutritional circumstances throughout their lifespan to see whether animals with different types of intake have any significant difference in total life expectancy in patterns of mortality, and this is paying off very well.

Quite characteristic forms, for instance, of enzyme activity in the liver can be identified as being characteristic of certain stages in life of the rat, and these can be shifted to a younger or earlier pattern, say to a younger pattern of activity, by maintenance throughout life on a diet that is low in both carbohydrate and protein. Also animals maintained throughout their lifespan have quite different patterns of renal disease and tumor formations.

The advisory groups we have had review this were quite excited about the work.

I think, more generally, I might state that our objective in aging really is an attempt to understand the basic biological, behavioral and social processes that account for the gradual decrease in vigor and fitness that we all experience simply with advancing age, rather than being concerned primarily with the diseases that are important to old people. Obviously the diseases that are important to old people make up a major part of the total National Institutes of Health program.

We were able to identify in the present activity of the NIH about $2.5 million of research grants, about 51 projects, that seemed to be focused quite specifically on this matter of the effects of aging, rather than the illnesses of the aged.

Interestingly enough, we were only able to identify three training projects in the whole country that were appropriate for transfer: One at the University of Chicago, one at Washington University in St. Louis in psychology of aging, and one in Pittsburh relating to the department of anatomy. There clearly seems to be a lack of research training in this field.

I would also like to illustrate a couple of other interesting areas of research that are going on that we have had an opportunity to review with technical committees. I do not consider myself a real expert in this field, but we have expert people in this field. One, Dr. Robert S. Chang, at the School of Public Health at Harvard, has been able to develop tissue culture methods for handling cells that are not dividing rapidly. Most of the cells used in tissue culture work do divide too rapidly to be useful for properly studying the aging process at the cellular level. But by using slowly developing cells, he has been able to tease out some of the basic biochemical and metabolic activities of aging at the cellular level.

BROWN UNIVERSITY PROJECT

A third project we have had the opportunity to review is one that you may be acquainted with at Brown University where they have done a very good job of——

Mr. Fogarty. I was going to ask you about that, because you mention it on page 76 of your justifications.

Tell us just what you are doing there.

Dr. Harting. Well, they are embarking on a difficult type of research, research that involves virtually establishing a population from a community so that with the examination of a relatively small number of people, one can be sure that one is really characterizing the total population. This is a difficult kind of population sampling work and, although they do not have much in the way of substantive results that I can describe to you, I think that they have been successful in the job of getting the sample identified and obtaining good interview data from this population of 600 people. The males of the family units were between age 60 and 64 in the year 1960. These investigators are trying to find out such things as the nature of the effects of retirement on older people, the effects at this age on mobility, of various kinds of health problems, and the differential social effects of illness as a function of, say, retirement status.

Mr. Fogarty. You think they are doing a good job as far as they have gone?

Dr. Harting. I not only feel this from my own professional opinion, but the review group that we had reviewing this with us this fall felt sufficiently enthusiastic to recommend that we supplement the funds available to be able to expedite getting analyses from the data that are at hand.

MENTAL RETARDATION AND INFANT MORTALITY RELATED TO POVERTY

Mr. Fogarty. There is one other question I meant to ask you on mental retardation. You mentioned the fact, the problem of cultural deprivation. How does this relate to the poverty program? I should call it the antipoverty program.

I remember some of the figures from a study which was made in Chicago showed that more mental retardation occurred in the slum areas. It was quite a significant difference. This ties in with this antipoverty program.

Dr. Aldrich. We have given some thought to this, Mr. Chairman. In many areas of the country where socioeconomic levels are depressed, I think generally you find a poorer quality of offspring. There is probably a higher incidence of malnutrition, and you find higher infant mortality rates by far.

Incidentally, it is my personal opinion that the relatively high infant mortality rate in the United States—as measured against the rates of other Western nations—could be lowered by improving conditions in these depressed areas with very high mortality rates. This ties in to the antipoverty program quite definitely.

There is pretty good information to the effect that malformations are more prevalent where mothers have poor nutrition and do not have adequate care, and they also have more premature infants.

To answer your question specifically, we are interested in the antipoverty question not just from the standpoint of mental retardation, but from several other program areas.

FELLOWSHIP PROGRAM

Mr. Fogarty. You are cutting back in your fellowship program from 220 to 217. Why is that?

Dr. Aldrich. An increase in stipends.

Mr. Fogarty. You are cutting back?

Dr. Aldrich. We are cutting back because we have to provide funds for the increase in the level of each individual stipend, thus cutting back the number that can be supported.

Mr. Fogarty. If you had more money, you would not have to cut back?

Dr. Aldrich. No, sir.

TRAINING GRANTS

Mr. FOGARTY. Your justifications emphasize the shortage of trained personnel in the various fields in which you work but you are reducing the number of training grants by 1—from 89 to 88. It does not make sense to me.

Dr. ALDRICH. We feel we can make some additional training awards. There will be a few that will terminate; and there will be some funds available to fund new ones from this. But I certainly agree emphatically that the need for training in some areas, particularly in aging, which has been emphasized, is paramount.

Mr. FOGARTY. I agree with you, this is one area you ought to be going up 15, 20, or 30 percent, and get the money for it. But if we only give you the money you ask for, there is not much you can do about it.

DEVELOPMENTAL SCIENTIST PROGRAM

What is this new experimental training program to prepare developmental scientists?

Dr. ALDRICH. This is very closely allied to the medical scientist program Dr. Shannon described yesterday.

Mr. FOGARTY. What is your definition of a medical scientist?

Dr. ALDRICH. My definition is a person who is trained broadly in medicine and biology, and who starts synthesizing this background from a much earlier period of life, preferably starting during the latter part of his undergraduate college or university training period and carries on forward through the usual years of medicine and postmedical preparation.

When I say "trained broadly," I think today the young investigator has to have a great deal more background in mathematics, physics, in genetics, and in the social and behavioral sciences.

There was some discussion yesterday of psychology, anthropology, and sociology. I am sure these scientific disciplines would be a strong asset, balanced with the background in physical sciences. Young future scientists should have a great deal more training in the field of genetics and embryology. For example, Mr. Fogarty, embryology as a discipline with an administrative focus in medical schools almost disappeared from the Nation's medical schools some time in the late 1920's and 1930's. This is one of the biggest problems today. We have to reintroduce this subject somehow into the scientific preparation of medical scientists. So our developmental scientist program is an effort to anticipate the Nation's needs for the future scientists who will give leadership in human development by providing them with a broad base in the physical sciences and in the behavioral sciences as well as expanded opportunities in embryology and other biological disciplines.

Mr. FOGARTY. The same exists in the medical schools as far as emphasis on strokes is concerned, we have been told.

Mr. Denton.

Mr. DENTON. This is the first year you have asked for the appropriation.

Dr. ALDRICH. Yes.

Mr. DENTON. Last year transfer was made out of other funds of $34 million.

Dr. Aldrich. Yes, sir.

Mr. Denton. This year you are asking for $43 million.

Dr. Aldrich. Yes, sir.

Mr. Denton. I was looking over some of these transfers: Cancer Institute, $1.146 million; and National Heart Institute, $4,981,000. How do those subjects relate to the work that you are doing?

RELATION OF CANCER STUDIES TO ACTIVITIES OF THE INSTITUTE

Dr. Aldrich. Let's take the National Cancer Institute transfers.

Mr. Denton. Yes.

Dr. Aldrich. We, as I mentioned earlier, sat down and literally went through all of the grants that the National Institutes of Health hold. Not once but three times. We separated out those grants which seemed to be intended to explain problems of child health and human development and which we thought were areas most appropriate for us to work in.

One of the things cancer research has been concerned about and interested in is how cells grow and how the cells divide and differentiate. So that in a broad sense over the years, the Cancer Institute has supported a good deal of research that has to do with the development of organ systems and could be termed embryological research. This is related to cancer very definitely; but with this new Institute, it is more related to our Institute than it is theirs. It is not a black-and-white situation very often, but it is more appropriate that it be supported by this Institute because it is primarily intended to throw light on how cells develop or how organs develop.

We had to deal with each grant application individually and decide on the basis of what the investigator wanted to do whether it was highly relevant to our Institute.

RELATION OF HEART RESEARCH TO ACTIVITIES OF THE INSTITUTE

Mr. Denton. I would not ask you about all of this, but tell me about Heart; how is that related to what you are doing?

Dr. Aldrich. I can use an illustration from the National Heart Institute. They supported a good deal of very fine work on certain aspects of pregnancy. There are some disorders that happen only in pregnancy, for example, the toxemias where mothers develop high blood pressure and also some changes in their kidney function. We are extremely concerned about the effects of toxemia on the unborn fetus. So when we talked over these grants with the Heart Institute, we had to decide whether the investigator was primarily seeking to determine the cause of high blood pressure and the changes in the arteries. If this was so, this was quite appropriately down the Heart Institute's main line of interest. If, on the other hand, they were studying toxemia in the broader sense and were more interested in the effects of the toxemia on the placenta or on the fetus, then this would be more appropriate for our support. So this is how we defined the differences between the two Institutes.

STUDIES ON AGING

Mr. DENTON. Now, about studying the arteries, I was going to ask you about that question. So many cases when people get old they get hardening of the arteries and have strokes and a great many of them become mental cases. It occurs earlier in some people than it does with others. Did you make a study of that question?

Dr. ALDRICH. The answer to your question is no, but we are very much interested in initiating some very long-term lifespan studies. This lies in the future, sir. But the question has been quite properly raised whether there is a relationship between hardening of the arteries and the kind of nutrition, for example, that the young infant gets during his first couple of years of life. I think that this is an important problem, but it is certainly one that we do not have any answer to.

Mr. DENTON. A lady doctor who was in here last year, I guess it was, said female hormones was a remedy for that.

Dr. ALDRICH. It may be nice to pick your parents, too, because there is a genetic factor.

Mr. DENTON. I have seen many people, maybe it is just lately, and I guess you would call it mental, because they get old and cannot remember anything.

Dr. ALDRICH. Yes.

Mr. DENTON. And it comes from hardening of the arteries.

Dr. ALDRICH. This is one explanation. But it may not be the only reason. When we were talking about learning earlier——

Mr. DENTON. Yes.

Dr. ALDRICH (continuing). This is a very interesting phenomenon, people do have different capabilities to learn at different stages of life. When we say we are interested in intellectual development, we mean we will also be studying the capabilities of middle-aged people to continue their intellectual development.

Mr. DENTON. That is all.

Mr. FOGARTY. Mr. Michel.

STUDIES ON REPRODUCTION BIOLOGY

Mr. MICHEL. Doctor, sometime ago I read where the National Institutes of Health reported that they were spending $3,426,135 on 198 research projects related to birth and population control. The article quoted someone as saying that the work in this field continues to reflect the "preoccupation of this agency with basic research on reproduction and with disease, rather than with birth control as such." Then it goes on to say what is being spent in this overall area.

I notice that the bulky report details some 758 research projects ranging from a $6,300 study of "reproductive behavior and flock organization of female turkeys" at Pennsylvania State University to a $38,640 experiment testing "antispermatogenic compounds on prison volunteers in Oregon."

What amount in grants would you say from your shop would be detailed to this area of reproduction, birth control, or whatever you call it?

Dr. ALDRICH. Well, let me try to answer your question in parts, sir.

Mr. MICHEL. All right.

Dr. Aldrich. Specifically, in the reproduction biology program, we estimate that we will spend about $4.2 million in 1964. In 1965, we propose to increase this to a figure of $5.5 million. These are estimates, of course. So this is an increase of approximately 33 percent in funding for 1965.

The reason why we are thinking that we ought to do this is because there is such a lack of basic fundamental knowledge about reproduction. Just to tick off a few of the things we do not know, we do not know the details by which there is union of the male and female cells. We know something about it in marine animals, we know something about it in guinea pigs, but in the fine details of this first step in reproduction are still hazy.

We just do not have solid answers to some of these fundamental questions. To me, one of the most intriguing areas is what happens after the union of the two cells? During the first few cell divisions is a very delicate stage of life apparently and almost anything that goes wrong may interfere with normal implantation and later development of the placenta.

I suspect a lot of the problems we face up to when a baby is born may have taken place at a very early stage in life. So this means we are going to have to go into fairly substantial experimentation, obviously, with mammalian species other than the human being. We can use guinea pigs and monkeys extensively.

I am thoroughly convinced we have to support biological reproduction on a broad base and very vigorously.

We are not at the present time intending to support application of these things to population control. This is a matter outside the primary goals of this Institute.

Dr. Shannon. May I comment?

Mr. Michel. Go ahead.

Dr. Shannon. I would like to speak more broadly for NIH.

We fully accept that there is a very broad relationship between population growth, population dynamics, and human and embryo development. But population growth and populational dynamics are not our problems as a technical organization. Those general problems are really related more to the socioeconomic field rather than the medical field. But medically we can view certain aspects of the population problem as basic problems of fertility and reproduction.

Now, in relation to birth control as such, information on fertility and reproduction is very invaluable to those who wish to control the rate of reproduction or prevent conception by a variety of means. But again, the means used to do this should be determined not only on medical grounds but also in terms of social mores.

So this birth control, or more conventionally "family planning," involves the use of this total aggregate of information which, in Dr. Aldrich's program, is derived because of his preoccupation with problems that are essential for general understanding of reproduction and the factors which can introduce disease abnormalities, and so on. So that the basic work that is done is applicable to a number of areas, some of which are appropriate to a Federal agency concerned with medical research, others suitable for other objectives.

Our problem is to try to retain a program of sufficient vigor in the areas of biology and reproduction for our purposes without being distracted by the practical application being sought by other groups. Or, for that matter, without being fearful of entering these areas because of the possibility of criticism.

Mr. Michel. Does the real impetus in this area come from within the medical profession itself or are we being pushed into it by these forces on the outside that say we should or should not be doing certain things?

Dr. Shannon. It is derived from forces generated from within in an attempt to overcome our own ignorance of the very important biological processes that have profound effect on human health.

I should think we should concentrate on health knowledge aspects, and not be pushed into working for some socioeconomic purpose, or, on the other hand, be afraid to enter the field because of criticism. We ride between these two forces. When you operate in an area where you are going to have adverse criticism from either side, then it is most important that your program express your sound technical judgment of what is needed for your own program and that you be aware of these other forces but not subservient to them.

RESEARCH ON REPRODUCTIVE BIOLOGY IN FOREIGN COUNTRIES

Mr. Michel. You say on page 7 that research in reproductive biology is relatively strong in foreign countries, especially Scandinavia, Japan, and Western Europe.

Let's take Japan, for example. Are they definitely further along in this area than we are?

Dr. Aldrich. Let me answer your question.

Mr. Michel. Can we gather the same information from them that we would be expending money for here?

I was over in Japan attending a conference in January again and I know from previous visits there, and from reading, what the general trend of population growth is. Apparently their population growth is down now to just a very slight annual increase.

Now, with that little preface, will you respond in any way you wish.

Dr. Aldrich. I can respond. I have been thinking about this a good deal during this year.

I believe that the Japanese became interested scientifically in problems of reproduction because they were faced with an enormous population problem. They were also at the end of the war rebuilding their scientific centers and medical schools, and many of the young people, as young people will, identified with the most pressing problems of the nation. Of those that happened to go into biology and medicine, some became interested not only in basic biology of reproduction, but also in the generation of malformations. I think possibly the nuclear weapons business stimulated some of this interest. So that in Japan, there is some good research going on.

I do not mean to imply that there is not research in this country that is just as good or just as strong, but there are some extremely good people in Japan.

I think I might just for a moment illustrate also the same phenomenon, but with different manifestations, in England where in the field of reproduction they have one or two centers which are outstanding. They have done something that I think perhaps we might emulate in this Nation. For example, at Cambridge, they have one unit on reproductive physiology and biochemistry where they have very carefully brought together the veterinarians, the veterinary scientists and other scientific resources of Cambridge, with the proper animal resources of many kinds of mammalian species. Even the design of this center was special. The architectural design and planning was supported by a special grant and now they have really one of the finest units of its kind.

We have not set our minds yet in this country to bringing veterinary science together with our universities. Quite frequently you will find the veterinary school is 20 to 100 miles or more away from the university and the medical school.

In general, I am saying two things: There are some very good scientists in other nations working on important problems of reproduction, whether for social reasons or out of pure scientific interest. Also I think we can learn something from our friends in other nations about organization and how to go about research in these fields. We must use mammalian species and we can learn quite a bit from biological marine laboratories.

Scandinavia, Japan, Western Europe, I do not see how we can omit the scientific leadership of foreign nations in a field as important as reproduction. This is what I am concerned about.

INCREASES FOR 1965

Mr. Michel. Would this be an area in the whole research area of NICHD that we find the biggest increase percentagewise in 1965 over 1964?

Dr. Aldrich. No, sir. I would guess aging is probably the biggest, percentagewise.

Mr. Michel. Would you supply for the record the five areas in which you have the most significant increase in 1965 over 1964?

Dr. Aldrich. We will be happy to supply that for the record.

(Information requested follows:)

Program areas with most significant increases

[In thousands]

Program	1964	1965	Percent of increase
Aging	$3,650	$5,038	38.0
Congenital malformations	1,766	2,395	35.6
Reproductive biology	4,159	5,542	33.2
Perinatal biology	5,459	7,141	30.8
Growth and development	8,110	10,291	26.8

Dr. Aldrich. There are some areas where so little is going on that the increase will look enormous.

Mr. Michel. I appreciate that.

Dr. Shannon. One thing I would like to point out is that it is very difficult for us to make sound program projections at this time when the development of the program itself creates or brings to light new scientific problems.

Dr. Aldrich. Dr. Shannon, one thing that occurs to me in regard to this, is that the proper relationship between grants and contracts, too, may be a rather important matter in advancing this subject. I think the tools that we have to advance research in some of these relatively "have not" areas will need to be flexible.

We have had opportunities this year that I think we should have capitalized on by using contracts rather than grants.

Mr. Michel. That is all.

Mr. Fogarty. Is there anything else you would like to say, Dr. Aldrich?

Dr. Aldrich. One comment, if I may, sir.

Mr. Fogarty. Go ahead.

LIAISON WITH OTHER AGENCIES

Dr. Aldrich. I did want to bring out that we made a strenuous effort to work with all of the other governmental agencies with whom we have common interests. We have worked out a nice implementation of the liaison that was spelled out last year with the Children's Bureau. We have been actively working with them, I might say——

Mr. Fogarty. I did not ask about that.

Dr. Aldrich (continuing). On recruitment. We have been dovetailing our basic research program so that the utilization of this research would be in their hands, and their research on application of new knowledge will be expedited. We even have some built-in liaison through close acquaintance with their staff. So that this is, I think, a very cordial alliance.

We have also been working very actively with other branches of the Government. We hope to initiate this year a highly satisfactory arrangement with the Indian Health Service to explore some fascinating opportunities for research with them. I think before we started this morning, Dr. Shannon mentioned the very significant difference in mortality of infant American Indians, as compared to Negroes and whites, the American Indians being a relatively hearty race for the first 6 or 7 days.

I did want to put this in the record, we thought this had been a very enjoyable year from this standpoint, too.

Mr. Fogarty. Thank you, Doctor.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. KENNETH M. ENDICOTT, DIRECTOR, NATIONAL CANCER INSTITUTE
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
ROBERT E. LEARMOUTH, EXECUTIVE OFFICER, NATIONAL CANCER INSTITUTE
FRED V. SHAW, BUDGET OFFICER, NATIONAL CANCER INSTITUTE
B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH
DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
PUBLIC HEALTH SERVICE			
11 Personnel compensation:			
Permanent positions	8,272	9,320	9,736
Positions other than permanent	121		
Other personnel compensation	151	187	173
Total personnel compensation	8,544	9,507	9,909
12 Personnel benefits	875	950	994
21 Travel and transportation of persons	444	494	499
22 Transportation of things	150	96	96
23 Rent, communications, and utilities	283	312	312
24 Printing and reproduction	174	197	197
25 Other services	30,591	37,017	39,707
Payment to National Institutes of Health management fund	9,376	10,062	10,465
26 Supplies and materials	1,633	1,640	1,650
31 Equipment	741	760	725
41 Grants, subsidies, and contributions	68,395	73,776	75,326
Subtotal	121,206	134,811	139,880
Deduct quarters and subsistence charges	16	16	16
Total, Public Health Service	121,190	134,795	139,864
ALLOCATION TO VETERANS ADMINISTRATION			
11 Personnel compensation:			
Permanent positions	649	540	559
Positions other than permanent	128	124	127
Other personnel compensation	1	7	4
Total personnel compensation	778	671	690
12 Personnel benefits	55	47	49
21 Travel and transportation of persons	82	159	159
22 Transportation of things	3	3	3
23 Rent, communications, and utilities	1	1	1
25 Other services	32	35	35
26 Supplies and materials	50	107	150
31 Equipment	184	169	105
32 Lands, and structures	4		
Total, Veterans' Administration	1,189	1,192	1,192
Total obligations	122,379	135,987	141,056

Personnel summary

	1963 actual	1964 estimate	1965 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions	1, 266	1, 320	1, 344
Full-time equivalent of other positions	17		
Average number of all employees	1, 198	1, 234	1, 244
Employees in permanent positions, end of year	1, 224	1, 309	1, 327
Employees in other positions, end of year	33	0	0
Average GS grade	7. 2	7. 3	7. 3
Average GS salary	$6, 653	$7, 064	$7, 214
Average salary of ungraded positions	$4, 161	$4, 230	$4, 313
ALLOCATION TO VETERANS ADMINISTRATION			
Total number of permanent positions	113	99	93
Full-time equivalent of other positions	11	10	10
Average number of all employees	116	96	96
Employees in permanent positions, end of year	102	86	86
Employees in other positions, end of year	29	27	27
Average GS grade	5. 3	5. 4	5. 3
Average GS salary	$5, 220	$5, 481	$5, 484

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	58,701	60,902	62,384
(*b*) Fellowships	2,276	3,942	3,942
(*c*) Training	7,418	8,932	9,000
Total, grants	68,395	73,776	75,326
2. Direct operations:			
(*a*) Research	16,148	18,087	18,596
(*b*) Collaborative studies	28,741	41,174	44,184
(*c*) Review and approval of grants	1,751	1,920	1,979
(*d*) Program direction	852	860	877
(*e*) Cancer research facility	41	170	94
Total, direct operations	47,533	62,211	65,730
Total program costs, funded [1]	115,928	135,987	141,056
Change in seected resources [2]	6,451		
Total obligations	122,379	135,987	141,056
Financing:			
Comparative transfers to other accounts	10,429		
Unobligated balance brought forward	−307	−264	−94
Unobligated balance carried forward	264	94	
Unobligated balance lapsing	22,932	7,341	
New obligational authority	155,697	143,158	140,962
New obligational authority:			
Appropriation	155,742	144,340	140,962
Transferred to—			
"Salaries and expenses, Office of the Surgeon General" (42 U.S.C. 226)		−15	
"Operating expenses, Public Buildings Service," General Services Administration (76 Stat. 728 and 77 Stat. 436)	−45	−21	
"National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−1,146	
Appropriation (adjusted)	155,697	143,158	140,962

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[1] Includes capital outlay as follows: 1963, $1,177,000; 1964, $929,000; 1965, $830,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $22,186,000 (1963 adjustments, −$36,000); 1963, $28,602,000; 1964, $28,602,000; 1965, $28,602,000.

Mr. FOGARTY. We will now take the Cancer Institute.

Dr. Endicott, you may proceed.

GENERAL STATEMENT OF DR. KENNETH M. ENDICOTT

Dr. ENDICOTT. Mr. Chairman, I have a fairly long opening statement.

Mr. FOGARTY. We shall put your complete statement in the record, and you may summarize it.

(Dr. Endicott's prepared statement follows:)

Mr. Chairman and members of the committee, for the past 2 years I have been reporting to this committee progress being made in linking viruses to human cancer. Last year I explained why we attach such importance to research into chemicals as a cause of cancer and described advances being made in treating childhood leukemia.

This year I would like to give you some of the reasons we are increasingly optimistic about the opportunities in these fields and the role newly developed instruments are playing in advancing our knowledge. Since this committee has played a leadership role in attacking cancer, I believe you will be gratified to know that leukemic children are being sustained with transfusions of infection-combating white cells and hemorrhage-preventing platelets. This prolongation of life is especially gratifying, for their disease is being kept in remission for longer and longer periods with combinations of drugs administered to the body, including injection into the fluids surrounding the spinal cord and the brain itself.

Before commenting on developments in these fields more specifically and touching on the smoking problem, I would like to relate how we are changing the National Cancer Institute, why we are doing so, and the importance of the changes being made to the earliest possible solution of the cancer problem. We believe that the developments in the research areas mentioned are so improtant and so opportune that we must do everything feasible to push forward now. Moreover, we have gradually acquired experience in working with industrial concerns and with directors of other cancer institutes. These resources have developed so that a coordinated effort on problems is feasible—particularly when backed by the continuing strength of research components of medical schools and universities. Other developments affecting cancer research also make advances in cancer more promising. To explain something about these developments we must look at cancer research as it has been in the past.

With the establishment of the National Cancer Institute in 1937 the Federal Government assumed a research responsibility that was clearly beyond the capacity of the private or industrial resources then existing in the field of medical science. Cancer was recognized as a formidable problem which would require the best efforts of investigators in practically every area of biological science and medicine, and the followthrough of practicing physicians and public health administrators to bring the disease under effective control. The initial role of the National Cancer Institute was mainly to provide financial support for, and to encourage larger numbers of qualified scientists to undertake research related in one way or another to the problem of neoplastic disease. The field of opportunity was virtually unlimited. So little was known about the fundamental nature of cancer and its effect upon the organism in which it occurred that practically every scientific area could be expected to contribute important information. The Cancer Institute has made a large portion of its funds available for many different kinds of research that were not only basic to the cancer problem, but often to other health problems as well. This was done with the conviction that not much real progress against cancer could be expected until more was known about the biology and chemistry of normal life processes and the changes characteristic of malignant growth.

In recent years new institutes and new programs in the Public Health Service have come into being, and medical research funds have been sharply increased. Such developments in the Service have made it possible for a number of organizational entities to share the cost of studies important to all of biomedical research. All parts of NIH do so to some extent, but this point can be illustrated by mentioning the newly created Institute of General Medical Sciences. It provides a broad base for support of fundamental research and training in various scientific disciplines and specialties.

These activities of other institutes relate to the role of the National Cancer Institute in several ways. We may expect that programs such as those of the National Institute of General Medical Sciences will assume the primary responsibility for training manpower to the doctorate level of competence in the various scientific disciplines. The National Cancer Institute is therefore not required to support such a heavy training load and is particularly concentrating on advanced training, including training through its support of the research by men already trained in their particular disciplines. The actions of other Institutes, by relieving us of the necessity of supporting research more general in character, have slowed somewhat the upward trend in research important to cancer which needs to be supported through the National Cancer Institute grants program.

These developments are significant in themselves and in the effect they have on the Cancer Institute's role. The Institute will continue appropriately to be called on to support research, frequently basic in nature, of individual investigators, for this is essential to future progress. However, our staffs can now begin to devote more time to identifying, planning, and working with the Council to concentrate resources on aspects of cancer that offer promise of early practical results. By means of coordinated or problem-solving programs attempts are made to secure a concentration—of concepts, ideas, technical abilities from many disciplines, and resources—on certain identified aspects of cancer research. It should be stressed that even in resulting coordinated, planned research programs we will also be involved in basic as well as applied and developmental research. There will be times, and frequently, when we will need more basic information if we are to push forward. Nevertheless, selected areas such as research in leukemia, viruses, carcinogenesis, and certain forms of treatment are so important, so broad and so complex, that we must do more than provide project support to individual investigators. Teamwork by members of various scientific disciplines and provision of many resources in a more coordinated and integrated manner are required to make these areas move ahead rapidly. Therefore, rather than choosing between two common but somewhat opposing beliefs concerning research in cancer, we have decided that both approaches must be taken and often combined.

One belief often advanced by scientists is that we must understand cancer and the cancerous process before we can hope to solve the cancer problem. There is much to be said for this point of view. The physical sciences have made some of their greatest progress when certain basic facts and concepts were understood. We intend, therefore, to continue to support directly and through grants, basic research performed by scientists who are most capable and suited to provide enlightenment about cancer and the cancer process.

On the other hand, many scientists believe we cannot and should not await full understanding of the nature of cancer for the history of medicine is replete with examples of disease prevention and cures without complete understanding of the underlying processes. To this day we do not fully understand the way in which aspirin or digitalis or the tranquilizing drugs work to relieve symptoms or to cure disease. We therefore also intend to extend planned, coordinated problem-solving research programs.

In recent years we have learned to work with mechanisms for a planned approach to certain aspects of the cancer problem, as in cancer chemotherapy. We have adapted and changed our planned programs as we have learned more about the problems with which we are dealing. I will mention a little later how the cancer chemotherapy program is being changed. Last year I indicated we were establishing task forces in the viruses and leukemia areas and making a major reorganization of our activities to get on with a coordinated attack on the problems which confront us. We are now organized to tackle problems now clearly defined and adapting to meet those which we will face in the not too distant future. We await with impatience developments in the human virus area which will demonstrate that a virus is a causative factor in at least one type of human cancer. Our organization is being made ready for such a development because we know that when this happens we must exploit this lead with all possible speed. The necessity for making much greater research efforts on chemicals in relation to causation of cancer is already upon us. It has become clear that the growth of our industrial society and the complexities of modern living are exposing all of us to several possible cancer-causing chemicals. Our organizational framework for this area is established although only partly staffed.

While making major program and organizational changes during the last year or so we have been coldly reappraising our ongoing activities. Last year I froze a substantial share of our contract funds until we could be sure that the activities in which we are engaged were moving in the right direction and that we had the mechanisms to guarantee that our concentration of effort was in the areas of greatest importance. In addition to the task forces, I established a group of Associate Directors, a Scientific Directorate, and five scientific review committees. As a consequence, during this reorganization, reexamination, and reappraisal, we lapsed substantial portions of the funds made available by the Congress. I am pleased to report that this new organization is going well, particularly in giving a sense of common purpose, and am convinced that in the future it will go even better. As of December 31 all contract funds have been earmarked specifically for approved programs which have passed our Committees and Scientific Directorate, and which have been carefully outlined to the National Advisory Cancer Council. Our grant funds are also earmarked. The problems confronting us for the balance of the year will involve administrative aspects of grant awarding and contractor selection.

The new coordinated and problem-solving approaches also involve cancer institutes, universities, and medical schools, but most of the burden of getting these things underway must inevitably fall on our own scientific and administrative staffs. We have incorporated into our concepts the need for maximum flexibility for ability to adapt to changing situations is essential. In summary, we know the programs we wish to push, the concepts to follow, and while still looking for some key personnel we are in a good position to move with dispatch. Now I should like to tell you about the research which I touched on at the beginning of this statement.

TREATMENT OF LEUKEMIA

The state of the art is so advanced in the treatment of leukemia with chemotherapy and supportive therapy that we feel justified in calling for an intensified, all-out effort toward the goal of cure of this hitherto invariably fatal form of malignant disease. The progress in research that has led to this stage has been one of the most rewarding experiences thus far in the long and determined battle against cancer.

Improvement in treatment has increased the remission rate for children with acute leukemia to about 90 percent and has dramatically increased the periods of their remissions and consequently their life expectancy. We are thinking now in terms of survival of years, as contrasted just a short time ago with an average survival of a few months for leukemic children, and we have now created a registry of patients surviving more than 5 years in order to keep an accurate count of such patients.

Studies of combinations of drugs have continued to bear out their promise of improved results in overcoming and delaying the development of drug resistance. Two drugs given together are sometimes more effective than each given alone, and many combinations, including combinations of several drugs at a time, are being explored. One of the clinical experiments we are watching with great interest and hope is underway at the National Cancer Institute using a combination of four drugs, each of which is capable of inducing temporary remissions of acute leukemia of childhood. These are vincristine, a periwinkle plant extract; prednisone, a synthetic steroid; methotrexate, a folic acid antagonist; and 6-mercaptopurine, a purine antagonist.

The use of combinations of drugs is an approach that has proved successful against other diseases. The antituberculosis drugs, for example, are only partially effective when given one at a time, but when given together they often cure the disease. Since cure is now the goal of therapy in the leukemia program a major objective is to reach and destroy all leukemic cells. That this is theoretically possible has been shown in animal model systems and in laboratory studies of leukemic cell populations both before and after treatment. One of the chief obstacles encountered in treating patients has been the difficulty of reaching leukemic cells that accumulate in the brain, since most drugs do not penetrate the blood-brain barrier. A few drugs are now available, however, that will pass from the blood into the central nervous system, and the utilization of these in combinations with remission-inducing drugs is being evaluated.

Chemical control over acute leukemia is one of the primary concerns of the acute leukemia task force, organized by the National Cancer Institute just over a year ago, and consisting of Institute and other investigators representing approximately 90 institutions with leukemia programs. The task force is working on the problem of which combinations and sequences of drugs now known to induce remissions of acute leukemia offer the greatest promise, based in part on animal studies, and on clinical studies already in progress. The task force is working also on developing ways of predicting therapeutic activity as well as toxicity of single drugs and combinations. A battery of three transplantable mouse tumors and one rat leukemia for predicting clinical activity, and an improved system for predicting clinical toxicity have resulted from the task force's efforts. Both systems are in use in the nationwide cancer chemotherapy research program, but it will take some time to assess their efficacy in identifying new and promising chemicals.

Control of hemorrhage and infection, the two most frequent causes of death among acute leukemia patients, is another important concern of the task force. The effects of blood platelet replacement as a treatment for hemorrhage have been so dramatic that acute leukemia patients being treated at the National Cancer Institute are given platelets as a preventive measure whenever their own platelet counts fall to dangerously low levels. Equally dramatic results have been obtained at the National Cancer Institute with transfusions of white blood cells of the granulocyte type to cure a particularly virulent and previously uniformly fatal type of infection in a number of acute leukemia patients.

The advantages of platelet replacement in enabling physicians to keep patients alive until drugs can take effect and to make greater use of drugs whose side effects include depression of platelet production are at present available in only a very few centers. The task force is taking steps under contractual arrangements to organize platelet transfusion programs in several large hospitals located in strategic places around the country. It is also working actively with the American Red Cross to improve platelet collection techniques and is planning a program of research on storage and preservation of platelets without loss of their viability.

Broad application of the benefits of granulocyte transfusions is limited primarily by the fact that the only practical source of granulocytes at the present time is a patient with chronic granulocytic leukemia, who has a surplus of these infection-fighting cells. To meet the obvious need for granulocytes from normal donors, the task force is supporting the development of a continuous flow centrifuge, so called because the donor's blood is drawn, the white cells removed, and the other elements returned to the donor while the blood flows in a closed system from a vein in one arm, through the machine, to a vein in the other arm. This procedure would make it possible to obtain from the blood of a single individual the granulocytes needed for one transfusion and now requiring more than 30 normal donors.

VIRAL ETIOLOGY OF LEUKEMIA

The Institute's decision to launch a major attack to achieve chemical cure of acute leukemia was based not only on a progressive advance of therapeutic capability but also a strong suspicion that acute leukemia is a viral disease offering the possibility of a combined attack from the standpoints of prevention and treatment. A disease-oriented approach focused on the entire problem of acute leukemia is therefore being undertaken through the avenues of established research in our own laboratories and clinics and through coordinated task force efforts. If successful in this venture, we shall have learned broad lessons applicable to the entire cancer problem.

The suspicion that leukemia may be a viral disease is strongly rooted in many laboratory findings over a number of years. Leukemia in fowl is known to be viral in nature. Leukemia and related disease occur so commonly in domestic fowl that they create an economic problem in the poultry industry. Over the last decade, a dozen or more types of mouse leukemia have been discovered and the evidence is increasing that perhaps all spontaneous mouse leukemia is viral in nature. Leukemia in rats also is due to viruses, and we have recently learned of a report suggesting that a lymphosarcoma in cats is virus-induced. Studies of animal leukemias continue to provide an important pool of knowledge of the mode of transmission of cancer-causing viruses and their mechanism of action.

A second important research area is concentrating on studies of "helper" viruses, without which certain cancer-causing viruses appear to be unable to produce infectious progeny. The first helper virus was discovered by an Institute grantee, who demonstrated that Rous sarcoma virus (RSV) of fowl can induce malignant transformation of chick embryo cells to sarcoma cells, but needs the aid of another virus, named "Rous associated virus," to produce new, complete RSV particles. The defect of RSV apparently derives from its inability to direct synthesis of its protein coat over its nucleic acid core. Since the protein coat determines whether a virus is immunologically acceptable to an individual host, that is, can infect the host, research has been conducted on combining RSV nucleic acid with other protein coats with the aid of various helper viruses. Tumors have been produced in this way in hamsters, rats, guinea pigs, and even monkeys.

This result raises the question of whether helper viruses may be involved in enabling various strains of RSV to cross species lines. All this adds up to a concern over whether a nucleic acid core from any virus properly combined with a human protein overcoat could become tumor-producing in man, and we now realize not only that finding human cancer-causing viruses is a big problem, but that we may also have to find helper viruses.

While continuing to probe for fundamental information, we are moving ahead with our intensive efforts to find human cancer-causing viruses. Blood specimens of acute leukemia patients are being examined for particles that might represent human leukemia viruses. This search stems from National Cancer Institute findings which showed that virus particles were present in the blood of laboratory animals in which leukemia had been induced by virus inoculation and, further, that these virus particles had a characteristic tadpolelike shape, similar to that of many of the viruses that infect bacteria. The studies are done with the electron microscope on samples of highly pure virus obtained by spinning the blood at high speed in a centrifuge. At first, particles similar in shape to those found in the blood of leukemic animals were found in less than 20 percent of the specimens taken from patients. Now, with the use of a centrifuge developed collaboratively with the Oak Ridge National Laboratory of the Atomic Energy Commission, the separation of virus particles from blood is so efficient that almost all of the patient specimens examined in a preliminary survey show these particles. These particles were not found in similar studies in normal individuals. Other investigations, conducted under National Cancer Institute grants, have also shown viruslike particles in human leukemic tissue and blood examined with the electron microscope.

Finding the particles in human leukemia sets the stage for the important research needed to demonstrate their cancer-causing activity. A direct method by which viruses are proved as the cause of tumors in animals, such as injection of a cell-free filtrate of a tumor into newborn animals of the same strain and observation of tumor development after a suitable interval, cannot be contemplated in man. It is necessary to resort to indirect methods such as, for example, growth of suspect viruses in cultures of human tissue and in newborn primates. Preliminary to and concomitant with the research to establish the cancer-causing activity of viruses is a comprehensive effort, now in progress, to develop and perfect effective techniques and test systems. This is an enormously complicated and expensive undertaking, requiring large amounts of virus and thousands of animals of various inbred strains and species, as well as those whose viral characteristics are defined.

The National Cancer Institute's human cancer virus task force is organizing several efforts to determine the causative relationship of viruses to human cancer. Consisting of Institute and other investigators representing a number of active virus-cancer programs throughout the country, the task force has a special opportunity for pooling of resources and talents and for development of collaborative programs. The group is presently concentrating on two major approaches to the human cancer virus problem: to determine whether viral agents comparable with those that cause leukemia in mice and fowl are associated with human leukemia and lymphomas, and to define virus and antibody patterns in patients with various other types of cancer in search of evidence that viruses may be involved as causative agents. The task force is also organizing a program for collaborating in testing of suspect virus; the plans will include a division of effort in propagating suspect virus in tissue culture, developing animal species not now available for task force programs, and jointly using primate or other large or excessively expensive animal test systems.

In anticipation of the time when human cancer virus will have been identified, the National Cancer Institute is planning the steps that will need to be taken to put knowledge into use for the saving of lives. In the course of protective vaccine development, virus will need to be grown in large quantities. The Institute is already supporting under contract a tissue culture operation to produce mouse leukemia viruses in large quantities, with a view to developing techniques for growing human cancer virus in quantity in human tissue culture. Plans are being made for phasing in the large tissue culture operation with the operation of the centrifuge developed in collaboration with the Atomic Energy Commission for the purpose of developing techniques for recovering essentially pure virus particles.

A second approach that will become possible with identification and isolation of human cancer virus will be development of drugs active against the virus. A drug known by the short name of IUDR, originally synthesized as a potential anticancer drug, has been shown as effective treatment for a virus-caused eye disease, which, if unchecked, leads to blindness. The same chemical compound interferes with vaccinia (cowpox) infection in animals and inhibits the induction of tumors in hamsters by adenoviruses. Studies to develop chemical compounds active against cancer viruses are in progress at the National Cancer Institute.

ENVIRONMENTAL CARCINOGENESIS AND PREVENTION

The increased risk to cancer of persons in special occupations has been recognized at least since the 18th century when Percivall Pott identified soot as the substance responsible for the high incidence of scrotal cancer among the chimney sweeps of London. Since the late 19th century cancer of the bladder has been recognized as an occupational hazard in the aniline dye industry. The occupational nature of lung cancer in miners of radioactive ores has also been established. However, the mechanism of action of the carcinogenic agent, the pathogenesis of the resulting cancer, and possible implication of genetic and other factors are still not clearly understood.

Moreover, the possibility of weak carcinogens acting over long periods of time is an additional complicating factor in environmental cancer in general. Currently observed changes in the incidence of several types of cancer—the rise in lung cancer and the decrease in stomach cancer, for example—may be a reflection of variations in the presence of weak carcinogenic agents. In the laboratory we need yet to develop a satisfactory methodology for the detection and study of such agents.

A second problem is that of multiple exposure. Most of our laboratory experience is derived from test systems exposed to a single suspect agent. But this is not the way people encounter possible cancer hazards. A man does not puff away on a cigarette in a sterile test tube. He takes long drags as he impatiently threads his way through heavy city traffic behind a bus whose exhaust fumes further irritate a sore throat perhaps caused by a virus. And the average smoker does this not once, or twice, or even daily for several weeks. He repeats this performance over a period of 20 or 25 years; and as he grows older, hormonal and tissue changes inevitably take place in his body.

It is obvious that identifying and freeing our environment of cancer hazards is not a task for one agency nor is it one which today's investigators can expect to solve in their lifetime. The National Cancer Institute, therefore, is cooperating with numerous other institutions and agencies in attempts to speed up laboratory experiments which will duplicate man's experience and take full advantage of the clues provided by epidemiological investigations.

Of great importance are the collaborative research arrangements that are being evolved with the Atomic Energy Commission at Oak Ridge, already mentioned, and with the Laboratory of Infectious Diseases of the National Institute of Allergy and Infectious Diseases. In these investigations, aspects of radiation and viruses will be added to those on chemicals, thus providing a triad essential for a modern approach to carcinogenesis. For example, the joint program at Oak Ridge will include studies in which animals will be exposed to some of the types of chemicals, radiation, and viruses to which man is constantly exposed. Radiation will be given both in doses large enough to produce cancer and in smaller doses corresponding to the low levels normally present in the human environment.

We have also just put into effect, under contract, a program of long-term biomedical investigations that will focus on the principles involved in the cumulative effects of pesticides and other chemical agents on organs of immature and adult laboratory animals. A part of this study will be devoted to the development of more refined and rapid techniques for evaluating in laboratory animals the cancer-inducing effects of environmental substances. This is needed if we are to avoid continuous inadvertent contamination of our environment.

Other cooperative studies in carcinogenesis grow out of the observation of cancer in wild or domesticated animals. The recently reported relationship between an epizootic of liver cancer in commercially raised rainbow trout and a change in their diet has focused attention on potential carcinogenic agents in their food. Because this problem seems to provide an opportunity to arrive at a better understanding of epidemiological factors and mechanisms involved in carcinogenesis—even though no threat to human health from trout cancer is believed to be present—the National Cancer Institute and the U.S. Department of the Interior have consolidated their support of research through funding and facilities, resulting in a frontal attack on trout hepatoma.

An outbreak of disease among young turkeys in England has caught the attention of a number of investigators. Moldy peanut meal in the diet of turkey poults dying of acute liver damage has been incriminated and the toxic and carcinogenic agent identified as aflatoxin, a fungus product. Aflatoxin has since been shown to cause liver lesions in young chickens, swine, horses, cattle, and rats. As far as human implications are concerned, there has been speculation that the moldy corn that is an important ingredient of the native diet might be associated with the high rate of liver cancer among the Bantus of South Africa.

Studies assessing the effect of aflatoxin on experimental animals are in progress both in this country and abroad. As a part of the National Cancer Institute's participation in this area of research, a contract has been awarded to scientists at the Massachusetts Institute of Technology who will isolate, characterize, and synthesize large quantities of aflatoxins for use by qualified investigators.

The essential coordinating role of the National Cancer Institute is well illustrated in this area of environmental carcinogenesis and prevention of cancer. The Institute is uniquely suited to plan and implement these broad, complex investigations. It is also in an unequaled position to procure and interpret research information from staff and other investigators and, when appropriate, make it available to the proper enforcement agencies.

THE SMOKING PROBLEM

Undoubtedly one of the most troubling aspects of the cancer problem today is the question of smoking in relation to lung cancer. For 10 years now, the evidence linking cause to effect has moved steadily toward further incrimination of the cigarette habit. People who smoke have been greatly worried about reports or statistical findings and the pronouncements of expert committees both in this country and abroad. Tobacco stocks have fluctuated alarmingly in response to these perturbations, and individuals have tried to swear off smoking either on their own or with the assistance of "cigarettes anonymous" movements or other aids. Meanwhile, cigarette sales and lung cancer mortality continue to rise.

To say that this problem is a complex one would be to risk the understatement of all time. Statistical studies have shown that more heavy smokers than light smokers get lung cancer, but that nonsmokers get lung cancer, too. These studies have also shown that more men smokers than women smokers get lung cancer, although women are newer to the cigarette habit than are men. Epidemiologists have found that people living in rural areas have a lower lung cancer incidence than those in urban areas but that when heavy smokers move from rural to urban areas they experience an increase in lung cancer susceptibility. Laboratory experiments have shown time and again that residual tar from cigarette smoke will cause cancer when painted on the skin of mice, although a connection between this and lung cancer in human beings unestablished. Examination of human lung tissue at autopsy has shown, however, that smokers invariably have more extensive damage than nonsmokers. These examinations have shown, for instance, that in the lungs of smokers the cilia—hairlike appendages that sweep the tissue surfaces clear of irritants—are destroyed, which suggests that accumulation of tar may consequently occur and may induce cancer.

From all the studies and discussions on the question of smoking and cancer has come the inescapable conclusion that the smoker is at greater risk to lung cancer, and undoubtedly to certain other diseases, than the nonsmoker. Once accepted, this conclusion does not, however, in itself provide the answer to the problem of smoking and cancer. It only provides a premise for the development of working hypotheses for further study.

From the research standpoint, then, we may consider that the investigation of environmental conditions related to lung cancer has hardly begun. This is not, of course, to disparage the cancer control efforts directed toward reducing smoking as an important preventive measure. Yet, there are many aspects of the problem that, upon thorough investigation, may reveal even more important steps to be taken in the related areas of medical practice and public health.

It has long been suspected, for instance, that smoking may not be as harmful in itself as in combination with other factors in an increasingly contaminated environment. The atmosphere in which people live in large regions of this and other countries is becoming seriously polluted with industrial effluents and the exhaust vapors of gasoline engines and residential heating plants. People who smoke intensify these conditions for themselves and contribute to atmospheric contamination for others. The situation is complicated by the increased amount of ionizing radiation to which the population is exposed, and the presence of viruses which, if related to human cancer, may be found to be the triggering mecahnism that induces cancer of the lung.

The nature of the smoking process itself also needs to be thoroughly investigated. Although the tar from cigarette smoke can produce cancer, some believe that other elements of the cigarette product, in the processed tobacco or the cigarette paper, may also be implicated in lung cancer causation as the products of combustion. Again, although the toxicity of nicotine does not seem to be a direct factor in lung cancer causation, it has been suggested that nicotine, as the habit-forming active principle of tobacco, should be regarded as involved.

Hypotheses suggested by these two general approaches offer many opportunities for research aimed at reducing lung cancer mortality either by rendering the smoking habit harmless or by reducing the environmental contamination to which smoking contributes. The National Cancer Institute, which has conducted and supported epidemiological and laboratory research leading to the conclusion that smokers have the highest order of susceptibility to lung cancer and that tobacco tar causes cancer, plans to expand scientific investigation which hopefully will resolve the problem for all interests concerned. As related earlier in this statement, the Institute is becoming rapidly involved in more extensive and varied programs of research in the whole area of carcinogenesis. As these studies are advanced, they will be addressed more and more closely to specific problems in the expectation of practical and useful results. This is, in fact, the pattern and the purpose of the Institute's mission toward the goal of reducing mortality from cancer—a mission which will be pursued through coordinated effort to achieve the earliest, most decisive gains possible.

CHEMOTHERAPY PROGRAM

As members of the committee will recall, the voluntary, cooperative chemotherapy program was organized in 1955 as an extensive, partly empirical search for new and better drugs with which to treat cancer. There were no known reliable predictive animal test systems at that time, and a selected group of tests, referred to as a "screen," were selected to obtain data to learn if compounds that showed anticancer activity might be of potential benefit to man. Gradually, after a few years of operation, this mass screening procedure began to move a large number of compounds through a stage of pharmacological study into clinical trial.

When sound data became available for the first time on this major scale, it became evident that the screening system of three mouse tumors against which thousands of compounds were being tested was not selecting very many that were superior to those already in hand for treating human cancer. The screen was then enlarged and diversified in the hope and expectation of picking up larger numbers of active compounds. The newly enlarged screen is only now beginning to operate on a satisfactory scale, and it will be necessary to wait for some time before the results become known. The next few years will tell.

While this is proceeding, another aspect of the chemotherapy program is evolving, however. As experience is gained in the clinical evaluation of old and new compounds, the opportunity is offered to take some of these drugs back into the laboratory for further testing to see how they might be improved. Some drugs can perhaps be modified to make them more potent; others might be more effective if they could be given in larger doses without undue toxicity or undesirable side effects. Still others might be made more useful in various combinations. As this procedure develops, we will have new drugs or modifications of drugs coming into clinical trial through two pipelines rather than one, and the prospect of increased progress in the treatment and hopefully the cure of cancer should be exciting It will not be a short, easy road, however.

In conclusion, much can be achieved through a coordinated effort where by cancer institutes throughout the United States, industry, universities, and Government agencies each bring to the effort special talents and capabilities. We must utilize planned attacks where the state of knowledge warrants it, and some areas appear to be ready for this additional form of attack. We must do so if we hope to solve cancer problems as quickly as possible. We realize that this must be done with care. We should not expect quick answers and easy solutions to such complex problems as these. The nature of cancer is such that an understanding of it requires well-trained and rigidly disciplined minds, an exacting technical ability backed up by adequate resources, and most of all the ability to examine research and clinical results with complete objectivity. Our files attest to this latter point for they are full of worthless "cures" and idle theories by those who did not have or did not use such abilities. Finally, the state of knowledge about cancer and the organizational structure of the National Cancer Institute have now reached a stage of development to permit a more unified, major attack on cancer.

The request for 1965 is distributed among program activities as follows:

Grants:	
Research	$62, 384, 000
Fellowships	3, 942, 000
Training	9, 000, 000
Subtotal, grants	75, 326, 000
Direct operations:	
Research	18, 596, 000
Collaborative studies	44, 184, 000
Review and approval of grants	1, 979, 000
Program direction	877, 000
Subtotal, direct operations	65, 636, 000
Total, 1965 appropriation request	140, 962, 000

Dr. Endicott. Mr. Chairman and members of the committee, I welcome the opportunity of discussing with you the developments of recent months in cancer research, and the prospects for strengthening our efforts against malignant disease.

ROLE OF NATIONAL CANCER INSTITUTE

The initial role of the National Cancer Institute was mainly to provide financial support for, and to encourage larger numbers of qualified scientists to undertake research related in one way or another to neoplastic disease. In recent years new institutes and new programs in the Public Health Service, by sharing the cost of studies important to all biomedical research, have enabled our staffs to begin concentrating on aspects of cancer that offer more promise of early practical results.

Even in resulting programs, however, we will be involved in basic as well as applied and developmental research. We have decided that both approaches must be taken and often combined if we are to meet our objectives. We know the programs we wish to push, the concepts to follow, and are in a good position to move with dispatch.

TREATMENT OF LEUKEMIA

Treatment of leukemia with chemotherapy and supportive therapy has increased the remission rate in children to about 90 percent and has dramatically increased the periods of their remissions and consequently their life expectancy. Combinations of drugs, each of which is capable of inducing temporary remissions of acute leukemia of childhood, are being explored as a means of reaching and destroying all leukemic cells.

The Acute Leukemia Task Force, while conducting drug studies, is also concerned with the control of hemorrhage and infection. Advances in blood platelet replacement are enabling physicians to keep patients alive until drugs can take effect.

The suspicion that human leukemia may be a viral disease has been strengthened by laboratory findings over the years. Evidence is present that there exist "helper" viruses, without which certain cancer-causing viruses appear to be unable to produce infectious progeny. We now realize that it may be necessary to find helper viruses as well as cancer-causing viruses.

The National Cancer Institute's Human Cancer Virus Task Force is concentrating on two major approaches: to determine whether viral agents in animals are associated with human leukemia and lymphomas, and to define virus and antibody patterns in patients with other types of cancer in search of evidence that viruses may be involved as causative agents.

To save lives at such time when human cancer viruses will have been identified, the Institute is already supporting a large tissue culture operation for protective vaccine development. Studies to develop chemical compounds active against animal virus disease are in progress.

ENVIRONMENTAL CARCINOGENESIS

In environmental carcinogenesis and prevention, the Institute is conducting studies that simulate man's experience and take advantage of clues provided by epidemiological investigations. This broad coverage will include radiation, chemicals and viruses as carcinogens. The Institute is uniquely suited to plan and implement these broad, complex investigations in cooperation with other agencies.

The implication of cigarette smoking in lung cancer suggests working hypotheses for further study. The National Cancer Institute is prepared to continue scientific investigation of smoking and other factors that hopefully will solve the lung cancer problem

CHEMOTHERAPY SCREENING PROGRAM

The chemotherapy screening program is now operating under a newly enlarged animal test "screen." In clinical chemotherapy, opportunity will be found for the laboratory retesting of compounds following their initial evaluation in patients. As this procedure develops, we will have more new drugs or modifications of drugs coming into clinical trial.

COMPARISON OF 1964 AND 1965 BUDGETS

In conclusion, Mr. Chairman, the request for the National Cancer Institute for 1965 is $140,962,000, as compared with the appropriation of $144,340,000 in 1964, of which $135,987,000 is available for obligation. The 1965 budget request provides for increases over the 1964 availability as follows: $1,482,000 for research grants; $68,000 for training grants; $509,000 for research; and $3,010,000 for collaborative studies. Other smaller but no less important increases are described in the budget justification.

Mr. Fogarty. Thank you, Doctor.

Taking into consideration unobligated balances, reserves, and transfers, you have $135,987,000 available for 1964 and are requesting $141,056,000 for 1965, for an increase of $5,069,000.

UNPROGRAMED FUNDS

Now, I understand you absorbed all of your increased pay costs under the new legislation and still have $7,341,000 of unprogramed funds. Is that right?

Dr. Endicott. Yes, sir; that is right.

Mr. Fogarty. Congress did not increase your budget last year; did they?

Dr. Endicott. No, sir.

Mr. Fogarty. We gave you what you asked for, except for a slight reduction in overhead allowances.

Where and why were you off in estimating your needs for 1964?

Dr. Endicott. Well, sir, I think I explained at the time of the hearing last year the estimates were in error not in the total amount so much as they were between categories. We had overestimated last year the amount which would be required for training grants and fellowships, and had underestimated amounts which would be needed in other areas.

Now, I think this was discussed yesterday in connection with reprograming. The Cancer Institute requested substantial shifting around of funds within its appropriation and in part this was permitted, but in part it was considered perhaps going beyond the intent of the Congress. So that we have an appropriation with a line-item spread, which was excessive in training grants, and fellowships, and less adequate in other areas.

TRAINING

Mr. Fogarty. Why was it excessive in training grants and fellowships?

I thought there was a real need in this area.

Dr. Endicott. Well, sir, this is something I believe I mentioned last year. The training of scientists for cancer research is somewhat different from the problem of training of scientists, let's say, for mental health research, in that there is virtually no specialty or scientific discipline which has kind of a 1-to-1 identification with cancer. You use biochemists, physiologists, surgeons, and so on. Their training, at least according to present views, which I share, is oriented along the lines of their scientific discipline. It is after they have completed their training as a biochemist or physiologist and really at the postdoctoral level or at the working level when they begin participating in cancer research as a trained person that they acquire the special knowledges and skills that relate to cancer research.

Mr. Fogarty. Why can you not step up this program?

Dr. Endicott. Well, sir, if I may take you back a little bit, a few years ago, the training funds which were available were available largely within the categorical framework. The departments needing training funds applied to the categorical programs in order to obtain support, even though in the case of the Cancer Institute they really were training a biochemist, not a cancer biochemist. That was the time when the general funds were either nonexistent or in very short supply. With the development of the National Institute of General Medical Sciences, with its budget, along with the development of a number of other institutes which do identify with a discipline, as psychiatry and mental health, and so on, the level of requests from the universities for cancer training funds have simply failed to increase as they were expected to. Our requests for fellowships and training grants are substantially below those of other institutes, and of the general program.

This does not mean that the cancer field is not getting its fair share of trained manpower. Because we get them into the cancer field really by the support of research, by providing research support after they have finished their disciplinary training.

The one area which identifies with cancer, the only one we can really point to, is therapeutic radiology. This is a specialty in which the use of radiation for treatment of cancer is the major occupation. We have a training program in that field.

The other area in which we have substantial continuing demands are from cancer institutes which are part of an educational institution, like the M. D. Anderson Hospital in Texas, which is part of the University of Texas, or the Sloan-Kettering Memorial Institute in New York City, which is part of Cornell. Now, their programs are mostly at a very advanced level, and by preference they apply to the Cancer Institute for their support. So that we really do not have very many customers, that is the truth of the matter.

Mr. FOGARTY. It seems to me there is something wrong here somewhere. This is the second leading cause of death, is it not? Cancer?

Dr. ENDICOTT. Yes, sir.

Mr. FOGARTY. I would think there would be more interest in this.

Dr. ENDICOTT. Well, there is plenty of interest in studying the disease. But the attitudes of the teachers are in favor of broad training in a scientific discipline rather than in a specific disease. I think that I can speak, let us say, for pathologists; I am a pathologist. In laying out a training program for a pathologist, even knowing that he is going to go into cancer research ultimately, I would insist that he be given very broad training in the anatomy of human disease, and not just in the anatomy of cancer. Without this broad training he would be hard put to it to be sure he was not confusing cancer with some other disease. That is generally true for most disciplines.

For these reasons, given half a chance to apply for noncategorical funds, the preceptor will do so because it actually fits in with the training which he is going to be giving. This does not mean that he does not provide training in the cancer field. Because, generally speaking, some training in cancer is included in the broad disciplinary training.

Mr. FOGARTY. You know, in these exchange programs, where doctors come to this country for a couple of years?

Dr. ENDICOTT. Yes.

NEED FOR PATHOLOGISTS

Mr. FOGARTY. It seems to me I have had more requests from hospitals to try to keep pathologists in this country, because they are so important to the hospital and to other doctors working in the cancer field.

I think they have all gone back. I don't think any of them have been kept here longer than the regular time.

Dr. ENDICOTT. This is a peculiarity, I think, of our medical specialty board system, you might say. The control over approval of residencies is a closely guarded, precious thing for each medical specialty, and they generally do not favor the special hospital.

The cancer hospitals in this country, then, have a great deal of difficulty with the specialty boards which generally do not approve cancer hospitals for more than a limited period of training, oftentimes as little as 1 year. This leaves the hospital in a fairly desperate plight for house officer staff, and they resort then to foreign medical graduates in order to have a house officer staff. If you go through the major cancer hospitals, you will find often it is difficult to converse with the house officer staff, because so many of them speak English with heavy accents.

Mr. Kelly. It is true, is it not, Doctor, that pathology is treated as a noncategorical training program at the Institutes?

Dr. Endicott. Of course. Of course.

Mr. Kelly. Yes.

Dr. Endicott. Now, you cannot do cancer research without pathology. The largest laboratory in the Cancer Institute is the pathology laboratory. They serve, really, as a kind of control for all of the biological and biochemical work, and they are the people who determine whether or not what is being studied is in fact cancer. So they are very essential in any cancer program.

RESEARCH GRANTS

Mr. Fogarty. Almost all of the so-called program increase is for research grants and collaborative studies. The increase for research grants is $1,482,000, but most of this is for increased overhead allowance and continuation of projects already started. There is an increase of one in the number of new projects to be financed. You would not call this very dramatic progress in this area, would you?

Dr. Endicott. No, sir; I suppose you would not.

Mr. Fogarty. I get upset with you people for not pushing some of these programs any faster than you are, especially in the cancer field. I do not know why you are not. This increase of one new project to be financed in 1965—this is one of the worst budgets with which the Cancer Institute has ever come before this committee.

Dr. Endicott. That is not just one new project but rather one more new one than we are supporting this year.

Mr. Fogarty. It is still one of the worst.

I think the people are willing to pay for this kind of research. They want progress in the cancer field. That is the way I find it back home.

It seems to me we are kind of leveling off, and that drive is not there any more in the Institutes of Health. I am very unhappy with this overall budget this year.

PROGRAMED CHEMOTHERAPY GRANTS PROGRAM

What are the "changed approaches to the administration of the programed chemotherapy grants program" referred to on page 103?

Dr. Endicott. Oh. The methods by which we have been administering and financing phase 2 and phase 3 clinical studies are in the process of being modified. At the same time, we will be cutting back on certain types of studies in which we have been studying the effect of drugs and surgery at the same time.

We still have not, I think, a really satisfactory approach to the problem. It is complex, because it involves a large number of institutions and cuts across many different specialties. There is quite a strong tendency on the part of the specialties to try to organize within the specialty. At the same time, in order to get a broad spectrum of different kinds of cancer against which you test a drug, you need to combine the activities of a number of specialties. There is a continual pulling and hauling between the two types of organizations.

This, we felt, has led to some inefficiency, some duplication, and we are reorganizing it now on a regional basis, with one in the west coast, one in the Middle West, and one on the Atlantic seaboard; and are moving away then from——

Mr. Fogarty. Where are these located?

Dr. Endicott. The headquarters are in Los Angeles——

Mr. Fogarty. Which school?

Dr. Endicott. UCLA; and in Madison, Wis.; and in Buffalo, N.Y.

PROGRESS IN LEUKEMIA

Mr. Fogarty. What progress is being made in leukemia?

Dr. Endicott. This, I feel, is the area perhaps where we are moving along most rapidly, and where the experts seem to feel there is the best chance of fairly spectacular progress.

First of all, on the therapy side, the gains over the past few years in survival time are quite spectacular. We now have a number of patients—there are more than 60 patients with acute leukemia included within our own study groups that have survived more than 5 years.

Mr. Fogarty. How many?

Dr. Endicott. More than 60. This was unheard of when I was a student. The percentage which go into remission has increased quite spectacularly within the past decade. Now 9 children out of 10 who come into the hospital, who are usually desperately ill, go into remission, and, to all intents and purposes, regain their health, go back home, go back to school, and so on, at least for a time.

Half a dozen drugs now are capable of producing remissions in a variety of combinations. My own scientific director seems pretty convinced that this disease will yield to chemical control, and perhaps in the not too distant future, as being a disease which is now completely incurable but perhaps within a relatively short period of time will be completely curable.

VIRAL CAUSE OF LEUKEMIA IN ANIMALS

The picture on the etiological side is really tantalizing. We have now established beyond any doubt that a virus infection is the major cause of Leukemia in animals, in quite a variety now of different strains of animals, and in quite a variety of different kinds of leukemias in the same animals. These animal leukemias make beautiful laboratory models, and one is able to develop techniques which you can then take and apply into man.

Now, utilizing the techniques that have been developed largely in the rodent, it is now possible, with the help of our new centrifuge, which has come along beautifully in our collaborative program with the AEC, to demonstrate the virus particles in virtually all patients with actue leukemia, and we have been unable to find similar materials in controls. We have yet to cause these particles to replicate outside the body.

I am waiting with bated breath right now to find out how an experiment is going to come out at the Pfizer Laboratory. They made a very interesting observation, quite by chance, that by combining cells from the thymus and the spleen in tissue culture, they were able to produce enormous yields of mouse leukemia virus in a test tube.

Moving along from this, they reasoned that if you could get cells from a fetus, human fetus, from the thymus and the spleen, and get them to grow in tissue culture, perhaps you could get the same result with human leukemia.

They have an excellent human spleen-thymus culture going and we have just sent them a pint of blood which has very large numbers of these particles from a patient. I really have my fingers crossed as to how this one will come out.

Now, what we will be able to do about it if we prove viral cause of human leukemia remains to be seen. But we are betting that we will be able to develop some kind of immunization procedure, again using the rodent leukemia as the model system. At Pfizer and at several other contractors, we are undertaking to produce the rodent virus in large quantity in tissue culture, with the hope and expectation that we will be able to develop something comparable to a vaccine.

CAUSES OF CANCER

Mr. Fogarty. Do you want to say something about the cause of cancer—smoking, pesticides, radiation, viruses, and so forth?

Dr. Endicott. Well, there certainly are many of them. Probably in nature they seldom act alone. The smoker is exposed to some radiation, he is exposed to virus infections, he is exposed to atmospheric pollution, he ingests carcinogenic chemicals in his food, and these interplay with a number of variables relating to the man himself, his genetic background, and his hormone balance. I think generations to come will have plenty to keep them busy searching for new causes, as they are developed, largely by man, in the form of new chemicals, and in searching out the interrelations and trying to discover a point of attack, so you can break the chain somehow and prevent the disease.

TOBACCO

It is a little disappointing, I think, having established pretty clearly cause and effect relationship with cigarettes, to see that this demonstration does not really solve the problem. People keep right on smoking.

Now, this then leads you into some secondary kinds of research, I think. In part, it is a motivational research and in part a kind of addiction problem, which would be more normal to Dr. Felix.

Mr. Fogarty. You seem to be throwing a lot of responsibility on Dr. Felix here today.

Dr. Endicott. Oh, yes. He is a very able man.

The tobacco problem presents a number of opportunities to approach the question of definitive identification, what it is, or what the combined things are that produce cancer; and, as Mr. Michel suggested, "developing baskets of tobacco which do not cause cancer." This, from the standpoint of control of disease, is an alternative approach if the educational approach does not work.

Mr. FOGARTY. We are talking about the causes now.

CARCINOGENIC PROPERTIES OF VARIOUS SUBSTANCES

Dr. ENDICOTT. Now, the Cancer Institute is interested in and has activities going on in the carcinogenic properties of pesticides or of poisons, of a variety of chemicals and drugs which are introduced into man's environment through one route or another.

Mr. FOGARTY. What about the charcoal-broiled steak?

Dr. ENDICOTT. Well, it is interesting you should mention that. I had a telephone call from one of our consultants last night, who was a little disturbed. He had had a paper on his desk which one of his staff was proposing to submit for publication, which reported very high concentration of carcinogenic materials in charcoal-broiled steak, and was seeking some advice as to what he should do under the circumstances, and wondering what kind of furor such a paper might produce.

This is not new. It has been known for some time. It has been demonstrated in several different laboratories that in cooking procedures in which fats are heated to high temperatures and incompletely combusted, that chemical carcinogens are produced in the reaction. So that it happens when you burn tobacco, it happens when you burn steak, and so forth.

Mr. FOGARTY. Suppose you cut all the fat off the steak before you burn it, would that help?

Dr. ENDICOTT. Well, sir, most steak has fat between each muscle bundle, so that it is practically impossible to dissect it. You can get the gross pieces off the edge.

Mr. FOGARTY. What about cooking potatoes in the ashes? Have you ever tried those?

Dr. ENDICOTT. Yes, sir; I have tried them—as a matter of fact many of the things I am fond of turn out to be carcinogenic.

Generally speaking, the greatest danger occurs when there are fats or related-type compounds, which are more prone to produce carcinogenic materials than carbohydrates or proteins.

Mr. FOGARTY. Is there anything else you want to say before we get to the treatment of cancer and the diagnosis?

COLLABORATIVE PROGRAM WITH AEC

Dr. ENDICOTT. I would like to make a brief report on our collaborative program with the Atomic Energy Commission at Oak Ridge. The first stage of renovation of the factory building has been completed, and research is actually getting underway on the top floor of the building, where we have constructed some large exposure chambers, where one can make prolonged exposure under carefully controlled conditions of large numbers of animals.

The remainder of the renovation will be completed during this year and next year and by the year after next the program ought to reach full operation.

At the same time, on a related but independent project, as a spinoff from AEC efforts to develop more effective means for separating isotopes by centrifugation, we have obtained a series of very unusual centrifuges which are performing beyond any of our expectations, from the standpoint of our ability to separate particles of different sizes in a quite precise manner in continuous flow. Quite remarkable concentrations of viruses are possible with one of these models, and it was with this model that the work was done on the separation of particles from human blood that I mentioned.

This is a very satisfactory arrangement with the Atomic Energy Commission, and I feel, really, that in view of the complex nature of environmental carcinogenesis and the inevitable interests of different Federal agencies in this problem, that perhaps the wave of the future, the pattern of the future may well be the development of centers of this kind which are financed by and operated jointly by several different agencies.

TREATMENT OF CANCER

Mr. FOGARTY. What progress is being made in the treatment of cancer and the diagnosis of cancer?

Dr. ENDICOTT. The field of treatment is moving along slowly. I already mentioned leukemia. There have been some drugs which have come along lately that are fairly spectacular in other diseases. The Wisconsin drug continues to be of great interest, 5 FU.

Mr. FOGARTY. We talked about it last year.

Dr. ENDICOTT. Yes, we have talked about it before. This drug has a very broad spectrum of action. I think it may well become the treatment of choice in cancer of the breast, for example.

Mr. FOGARTY. Why was it called the Wisconsin drug?

Dr. ENDICOTT. Because it was discovered there.

Mr. FOGARTY. Because it was discovered at the university in Wisconsin?

DRUGS FROM ABROAD

Dr. ENDICOTT. Yes. There have been several drugs this year which have come from abroad that are quite interesting. There is one from France which is quite spectacular in its effect on Hodgkin's disease, and it is also very interesting to us because it penetrates the blood brain barrier and gets into the central nervous system.

Now, this has been one of our most difficult problems in the management of leukemia, since most of the antileukemia drugs are kept out of the cerebrospinal fluid. They are unable to penetrate the barrier, and therefore never really reach the leukemia cells which are in the central nervous system. You get practically a complete cure, except in the central nervous system. This type of drug leads us to hope perhaps we may have a new tool.

COMBINED DRUG AND SURGICAL THERAPY

I do feel that I ought to report that the earlier enthusiasm for combined therapy, combined drug and surgical therapy of cancer of the breast was perhaps not warranted. As the studies have gone along in years, and the observation period has been extended and more patients have been admitted to the study, there is less and less difference between those who obtain surgery alone and those that have drugs with surgery. It may well be that when the study is all finished, there will not be any difference.

That is a somewhat disappointing result, naturally, because in the early stages of this study there was quite a substantial difference in favor of the combination therapy.

The surgeons are still very much interested in this approach, and there is quite a lively debate, really, between the surgeons and others as to just how far we should go in testing combination therapy. At the present time, I have very mixed feelings about it myself.

DIAGNOSIS

Mr. FOGARTY. What about diagnosis, is there anything new?

Dr. ENDICOTT. In the area of diagnosis, I do not really feel that there is anything worth highlighting particularly this year. There have been a number of technical advances, but nothing that I would want to point to as representing any real practical advance. As a matter of fact, the latest information which we have—and this has been obtained, to a considerable extent by the Bureau of State Services' program under Dr. Robbins (cancer control program)—the earlier optimism about mammography as a casefinding technique has given way to pessimism with regard to its use as a casefinding device. At the same time, it has continued to appear to be quite useful as an aid, as a diagnostic aid in patients in which cancer of the breast is suspected, as a tool to rule out or in, but not apparently as a screening device. It has too many false negatives and false positives.

Mr. FOGARTY. What I have heard so far has not been very encouraging as far as research during the past year in the cancer field is concerned.

BASIC KNOWLEDGE AND UNDERSTANDING OF CANCER

Dr. ENDICOTT. Perhaps I have erred in not discussing advances in our basic knowledge and understanding of the cancer problem. I have erred, perhaps, in limiting myself to discussion of obvious practical gains in the clinic.

If you look at it in those terms, it is a depressing picture, because the incidence continues to rise, and the cure rate stays about the same.

Mr. FOGARTY. I think you ought to give us the overall picture.

Dr. ENDICOTT. Perhaps you will permit me to submit for the record an answer.

Mr. FOGARTY. Put in the record what has been done to indicate we should continue spending these large sums on cancer research.

(Information subsequently furnished follows:)

THE CASE FOR CONTINUING AND EXPANDING FEDERAL SUPPORT OF CANCER RESEARCH

In the early 1920's, health officials began to be concerned about the increase in cancer deaths and a Public Health Service study published in 1925 demonstrated a steady annual increase in cancer deaths in the United States for every year from 1900 onward. This steady increase has continued to the present time. Although it is due in part to an increase in population and in part to the increasing average age of the population, as shown in the accompanying chart, there is an absolute increase which cannot be attributed to either factor. To only a very minor extent can the increase be attributable to improved diagnosis. The remaining increase must be attributed to factors such as the increase in lung cancer, likely due to cigarette smoking and other environmental factors, including chemicals, radiation, and probably virus infection.

In 1964, more than 290,000 Americans will die of cancer and, if present trends continue, nearly 50 million of the Americans now living will die of the disease. On a worldwide basis, as the diseases of filth and malnutrition are eliminated in the backward areas, cancer will increase even more spectacularly and may well reach an annual worldwide death toll of 10 million within the next several decades. Since the dawn of history, the diagnosis of cancer has created terror by virtue of its slow, inexorable progression, often accompanied by agonizing pain and not infrequently by repulsive disfigurement.

Concerned over the steady increase of this dread disease, the Congress in 1937 passed the National Cancer Act, creating the National Cancer Institute, first of the categorical Institutes which now comprise the National Institutes of Health. The legislative charter was extremely broad and the charge in effect was to eliminate the cancer problem. Beginning with a modest appropriation of $400,000 in 1938, Congress has steadily increased the appropriation to a level of $144,340,000 in 1964. In all, Congress has appropriated $1,017,759,222 to the National Cancer Institute in the hope and the expectation of an ultimate solution to the cancer problem. Has this money been well spent? Has any progress been made? Should the effort be continued? The answer to all three questions, in my opinion, is "Yes." To understand the reason for these affirmative answers, one must know something about the disease, about the general approaches to the solution of the problem, about the resources necessary and available to attack the problem, about the progress which has been made, and about the possibilities for the immediate and the long-range future.

THE NATURE OF CANCER

"Cancer" is a generic term for an entire category of perhaps several hundred different diseases, produced by probably hundreds of causes, but possessing certain features in common. Under the microscope, cancer is seen to consist of an abnormal and apparently unrestrained growth of cells. These abnormal cells invade and destroy adjacent normal tissues and organs, spread to distant parts of the body through the vascular system, and ultimately cause death. From a gross standpoint, the disease produces swellings or tumors, which increase in size and if near the surface often ulcerate and become infected. Pressure upon nerves produces intractible pain, invasion of the skeleton destroys bones which leads to fractures, invasion of blood vessels produces hemorrhage, etc.

In general, this phenomenon of abnormal growth called cancer falls in the category of chronic disease. The incubation period, that period between the application of the inciting cause and the appearance of the disease is long. In experimental animals and probably also in man, the incubation may be as much as one-half a lifetime or even more. In many instances, the causal factor need not be supplied in a large amount at one time, but may be equally or even more effective in minute continuing exposures. For example, although cancer may be produced by a single large dose of X-ray, it may also be produced by very small daily doses. This same effect is also seen experimentally with many of the more than 400 chemicals which have been shown to produce cancer. Long incubation periods are also seen in animals when the cancer is produced by viral infection and it is often no longer possible to find the virus when the cancer appears.

In addition to these external causes, internal factors such as heredity and hormone balance obviously play a part. For example, it has been possible by selective breeding to produce strains of mice with very high or very low rates of different kinds of cancer.

The great mystery in cancer research is how do these many diverse causative factors obtain the same general end result of abnormal growth. It has long been assumed by many that the episode which changes the normal cell into a malignant cell consists in an alteration of the genetic material which controls the inheritance of traits from mother cell to daughter cell, and also provides the basic information code for controlling the functions of a cell. The mechanism of inheritance, the ability of self-replication, and this control of cell functioning are perhaps the most fundamental properties of living things and are just beginning to be understood. Cancer, presumably an abnormality of these fundamental life processes, remains today as mysterious as life itself, although the rapid strides in molecular biology and genetics and biochemistry are beginning to roll back the mystery.

The treatment of cancer has consisted of destruction of the abnormal cells, since there is no known way of restoring the cancer cell to normality. Most commonly, cancer cells are destroyed by surgical removal of tumors, by killing them in place with X-ray or other forms of radiation, or by chemicals applied either directly or systemically. Utilizing these several forms of therapy, the doctor today is able to salvage one out of every three cases, but often only at the cost of disfigurement, since it is seldom possible to destroy the cancer without damaging the normal tissues and organs to some extent. For this reason it is probably not appropriate to use the term "cures," but to speak rather in terms of survival.

GENERAL APPROACHES TO THE CANCER PROBLEM

Throughout the years there have been two main schools of thought regarding the strategy of solving the cancer problem. One school of thought, which has largely dominated, holds that since the essential knowledge necessary for laying out a completely rational approach is lacking, cancer research should consist of a maximum number of independent explorations of various facets of the problem carried out on an individual basis, with highest priority being given to the most attractive projects and the best men. Under this strategy, considerable emphasis is placed on basic research as to the biology and chemistry of cell growth, reproduction, and differentiation. Extensive studies are made on various kinds of cancer in laboratory animals, along with many individual studies of the cancer patient at the bedside, and cancer phenomena in populations. Characteristically these studies involve one senior investigator with one or two assistants and technicians and the present cost of about $25,000 per year for each project. The management of this type of research is relatively easy and inexpensive and consists largely of making intelligent selections among the projects offered for support and maintenance of adequate accounting and administrative safeguards to see that the money is spent productively for purposes intended. Central planning concerns itself with estimating the demands and regulating the rate at which new scientists are brought into the field through training programs.

The other approach is variously called applied research, collaborative research, target research, or programmatic research. In the cancer field this is best exemplified by the chemotherapy program in which there is a clearly defined objective—the discovery of drugs for curing cancer—and in which there is central planning and management with the efforts of companies, of institutions, and thousands of scientists and clinicians integrated into a massive empirical search characterized by a preliminary screening in animals, selection of the most promising for trial in man, and utilization of the human responses to further guide exploration in animals.

A similarly engineered program in the cancer field. which is still at a primitive stage, is an orderly search for chemicals which produce cancer and the development of a means for eliminating these chemicals from the human environment through engineering or replacement with harmless substitutes.

The engineered approach, which was largely lacking in the early days of the NCI, is finding increasing use as the fundamental knowledge provided by the independent projects affords opportunities for planned attacks.

RESOURCES FOR CANCER RESEARCH

The most important resource for cancer research is trained manpower. In the United States today it has been estimated that there are approximately 10,000 persons at all levels engaged directly in cancer research, of which 2,000 to 3,000 have doctoral degrees. The training programs of NIH, aimed primarily at doctoral level scientists, have as their goal the doubling of the manpower pool between 1960 and 1970, or a net gain of 10 percent each year. These manpower programs must be planned well in advance and given sustained support, since the period of time necessary to turn out an independent investigator approaches 10 years after high school. Subordinate personnel, requiring a few months to a few years of training, can be turned out more quickly.

A second important resource is a base of knowledge which provides an underpinning of future work in cancer research. In the past 25 years this base has grown steadily, both in terms of quantity and increased understanding of biological systems, including cancer.

The next most important resource for cancer research would be physical facilities and equipment. It has been estimated that approximately 2 million net square feet of space is currently devoted to cancer research and that to accommodate the present rate of growth of the work force approximately 200,000 square feet of net space would need to be added each year, at an annual construction cost of $10 million.

The fourth major resource for cancer research is organization. At the national level there has been created an organization with 25 years of experience and a central staff of nearly 1,300 engaged full time in the planning, conducting, coordinating, analyzing, and managing of cancer research and cancer research training. This organization, with the help of the National Advisory Cancer Council and other consultants and advisory bodies, is increasingly capable of planning and executing larger, faster, and more effective cancer research efforts.

PROGRESS TO DATE

In the 27 years since the National Cancer Institute was created the salvage rate in cancer patients has been improved from 25 to 34 percent, with a net saving of approximately one-half million lives. Viewed in a cold statistical manner, a charge against the $1 billion appropriated by the Congress during that period would represent an investment of $2,000 for every life saved. But this type of analysis is very misleading because of the inherent long lagtime between basic discoveries and their practical applications in man. To a considerable extent, the improvement in salvage rate is attributable to the application of knowledge already available at the time the Institute was founded or accumulated during its early, smaller stages. A good example is the important reduction over the past few years in mortality from cancer of the cervix, attributable to the widespread use of the Pap test, first suggested by Dr. Papanicolaou in 1928 and definitively proposed in 1943, and not yet used fully for the population of women at risk. A substantial amount of effort from the Cancer Institute from 1950 to 1960 was devoted to simplifying and improving the method and adapting it for large-scale population screening, at the same time training cytologists to read the tests.

From a standpoint of salvage rate and improved methods of therapy, the greatest investments have been made in the field of chemotherapy. The results of these investments have yet to be reflected in the salvage rate. Thus far only one form of cancer, choriocarcinoma—common in the Far East but a relatively rare form of the disease in the United States—appears to have yielded to chemotherapy alone. Progress in the treatment of acute leukemia is beginning to be evident, but for most types of cancer the harvest of lives saved remains for the future.

In the field of prevention, causes of several forms of industrial or occupational cancer have been identified, and progress has been made toward eliminating these chemical factors from the industrial environment, thereby preventing cancer. Examples are the prevention of respiratory tract cancer in the chromium industry, prevention of bladder cancer in the aniline dye industry, and reduction of skin cancer in the petroleum industry. At the same time, much of our knowledge regarding prevention of cancer remains to be applied and, therefore, to have its effect felt. A good example is the case of lung cancer and cigarette smoking. Convincing evidence, both experimental and statistical, has been assembled in the past decade to show that excessive smoking of cigarettes is the major factor responsible for the sharp increase in cancer of the lung. Ultimately, these research results will lead to a reduction in lung cancer, but the precise manner in which this information is to be put to practical use will only emerge with additional research and development.

In terms of future application for the cancer field, the most important advances in recent years have come at the fundamental level. In the understanding of the life processes, tremendous gains have been made in our chemical and biological knowledge of proteins and the role which DNA and RNA play in the transmission of the genetic code and control of cell functioning. Many of these advances have come through studies of bacteriophage, a form of virus which multiplies in bacteria. Much of the knowledge has also come through studies in the lower forms of life such as molds or in highly purified artificial systems devoid of living cells. A number of things have happened in recent years which leads one to expect more rapid progress against cancer as these basic findings and techniques are applied to mammalian cells and to intact animals. Very recent studies indicate that the same general type of DNA-RNA control found in lower forms of life is functioning in higher forms including mammals. This new, fuller understanding of cell functioning now offers new possibilities for understanding how carcinogenic agents—chemicals, radiation, and viruses—produce the change from normal to a cancer state. The recent studies demonstrating that many forms of animal cancer are caused by viruses points up dramatically the importance of this area of research. These viruses are close chemical relatives of the DNA and RNA which control the life processes in mammalian cells, and some of these viruses are found in man. There are many reasons to believe that further studies of cancer viruses will make important contributions to our understanding of the basic mechanism of cancer induction. As understanding of these processes is gained, the probability of successful cancer prevention is increased, but it is likely to be a long hard road. As with other viral diseases, partial control may be possible through eventual development of vaccines.

In recent years it has become possible to cultivate mammalian cells in tissue culture and to maintain them through many generations in synthetic media. It has been possible to induce cancer in the test tube and to study the many complex factors of cancer induction one at a time in a relatively simple system. Viruses also can induce cancer in this manner, and, conversely, this technique is of great importance for producing viruses and vaccines.

Many other valuable laboratory model systems have also been developed, permitting controlled, precise studies which move much more rapidly than would ever be possible in man with his long lifespan and long cancer incubation period. The several hundred strains of inbred mice probably represent the most outstanding example of progress in laboratory models. There are strains of mice which have a predictable high incidence of a particular form of leukemia or breast cancer or liver cancer, etc. Such strains are especially sensitive to cancer-producing factors and are valuable tools for the rapid detection of weak carcinogens. These inbred strains are valuable also for providing uniform cancer material for laboratory studies, since the animals are sufficiently closely related within a given strain that a particular tumor can be transplanted from one animal to another, thereby making it possible to produce almost unlimited quantities of the same kind of cancer. These same strains of mice make it possible to screen anticancer drugs on a large scale by providing a uniform test system under which up to 1 million mice per year with identical types of cancer can be made available for testing thousands of different chemicals.

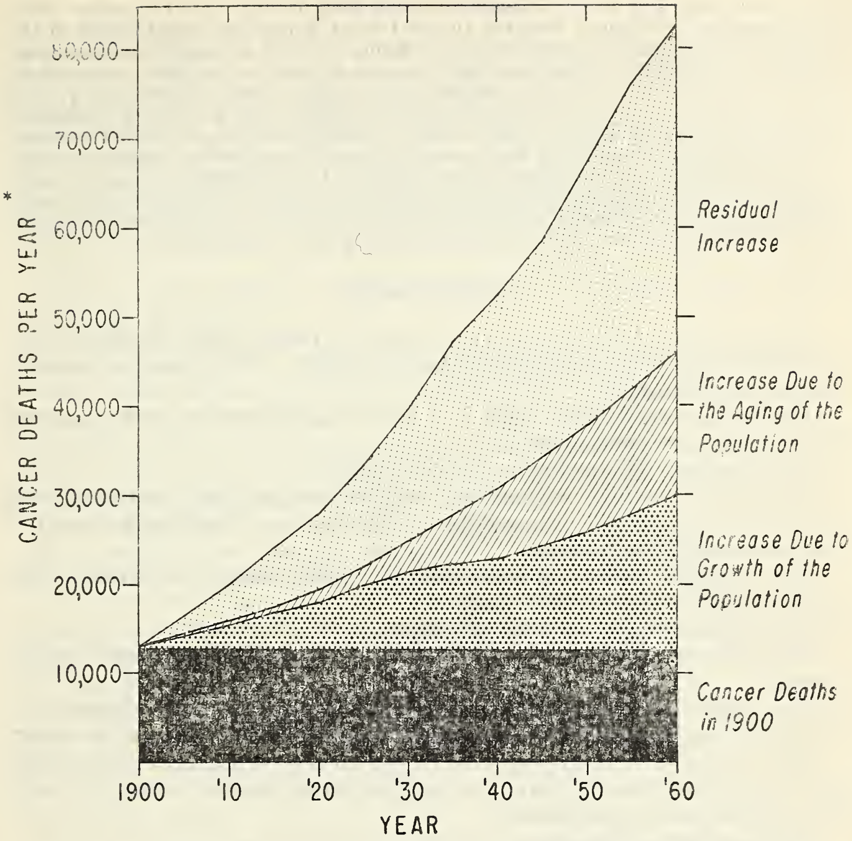
In addition to these important laboratory advances, much important baseline information has been accumulated regarding man. Statistical evidence has been accumulated showing marked differences in the incidence of different forms of cancer in different populations. Some of these differences are attributable to occupation, others apparently to geographic location, and others to race or diet or excessive sunlight, etc. In many instances the explanation for the differences remains to be discovered and constitutes an important lead for future research. Much knowledge has also been accumulated regarding the natural history of different forms of cancer in man and animals. Much has been learned about how cancer patients respond to drugs and to special supportive treatment such as transfusions of platelets to combat hemorrhage and white blood cells to combat antibiotic-resistant infection. Such fundamental knowledge will be valuable in the future as a baseline with which to measure the effectiveness of preventive and therapeutic measures.

OPTIONS FOR THE FUTURE

It is the responsibility of the Congress to determine the future magnitude and general structure of the Federal cancer research program. Three general options appear to present themselves. One would be to continue to expand the national effort by increasing the Federal appropriation each year. The budget which is before you proposes an increase of this year's expenditures, but is below the appropriation for 1964. I believe that the budget is modest and justifiable on sound scientific grounds, as well as on principles of sound management. The Congress has hitherto provided funds for training additional manpower and constructing additional physical facilities, and it seems a matter of good commonsense to utilize the manpower and facilities in which the Congress has already invested. Important, meritorious, promising research, both spontaneous and planned, is available for the increased investment of the Federal dollar.

A second option, and one which might be regarded as necessary for the sake of reduced Federal expenditures, would be to hold the line and limit the appropriation to the current level of expenditure. The principal danger in this approach lies in its long-range rather than its immediate implications. As research becomes more complex, it becomes more costly and a static budget often represents a cutback. Even more important, scientific manpower is in short supply and young men who have completed their training generally have a choice of several different fields of endeavor. They need not and will not stand idly by waiting for an opportunity to enter the field of cancer research, but will pursue some other endeavor and probably be lost to cancer research for the rest of their careers. Thus to stand still this year means to fall behind in the years ahead.

A third option would be to reduce the Federal investment. Such a step would have deleterious effects both immediately and on a long-range basis. The immediate effects would be to make it necessary to discontinue projects already underway and to lose the investments already made in them. The long-range effect would, I believe, be largely of a psychological nature with fairly profound effects on scientists' attitudes. Over the years cancer research has not been highly attractive to young investigators and clinicians. The research moves slowly because of the nature of the disease and the great length of each experiment. The chances of quick success are small and the opportunities to win fame appear greater in other areas. For the clinical investigator there is the added detraction of working with patients, most of whom die ugly deaths despite the doctor's every effort. Most young men enter the field for reasons such as cancer in their own families or an awareness of the great importance which society appears to place on the solution of this problem. I feel that such concrete evidence of a slackening of public interest as would be represented by sharp reduction in the Federal budget for cancer research would tip the delicate balance and sharply reduce for many years to come candidates for careers in cancer research.



***Figures are for 10 States and the District of Columbia reporting (Rhode Island, Maine, New Hampshire, Vermont, Massachusetts, Connecticut, New York, New Jersey, Michigan, Indiana, District of Columbia.**

SUMMARY

Proportionally, totally, and even after allowing for an aging population, cancer deaths in the United States are increasing. Of the Americans alive today 50 million will die of cancer if research does not reverse the trend.

The upward trend persists despite our ability to cure 50 percent of the cases and our actual experience of curing 34 percent when a few years ago we could only cure 25 percent of persons afflicted with cancer.

Cancer involves a basic life process, is a research area of awesome complexity, and confronts one with spans of time found in few other diseases.

The progress thus far in curing cancer is based on knowledge predating the founding of the Cancer Institute. The harvest of lives saved as a result of the tremendous body of knowledge acquired since then lies in the future. One cannot tabulate this knowledge for it fills libraries but one can mention a few areas.

We know that cancer is caused by chemicals in our environment to which we are becoming increasingly exposed and some have been identified. We have found that viruses cause cancer in animals and probably do so in people. The roles of DNA and RNA in cell growth and division are being slowly elucidated. We have new devices which separate out pure viruses and cell components for study. We find chemicals in increasing numbers which destroy cancers but are not yet curative and we know something about how they work. We are securing an increasing rate of regression in leukemia and for longer periods of time.

With the tremendous body of knowledge of cancer acquired over the years we can be optimistic that the current given picture will change. Organizations have been built and scientific leadership has been brought into the cancer field. The resources for cancer research in the United States are unparalleled in the world. To establish them has been an arduous task for, compared to other areas of medical research, findings are hard to come by and in the clinic one must be prepared to face heartbreaking suffering on a daily basis. Consequently, it is not surprising that many scientists find other fields more attractive. Congress has been in no small measure responsible for the building up of a cancer program which is gradually acquiring the knowledge needed to solve the cancer problem. It can provide funds to maintain this program, to accelerate it, or cut it back. If the latter, it should be fully aware that rebuilding would be slow and costly and even more so in terms of time than dollars, for cancer progress depends on scarce scientific talent which once lost cannot quickly be reacquired.

FELLOWSHIPS

Mr. DENTON. I notice you are requesting only enough funds to support 366 fellowships, which is 12 less than 1964. Why are you cutting back this program?

Dr. ENDICOTT. I think this is a modification necessary because of the change in stipend level, sir.

Mr. DENTON. What do you mean by that?

Dr. ENDICOTT. The stipend for each fellow has been increased and with the same amount of money available one has to reduce the number of fellows being supported.

Mr. DENTON. You are spending the same amount of money, but you are getting fewer fellowships?

Dr. ENDICOTT. Yes, sir; that is right.

Mr. DENTON. You need more money to keep that program on this basis?

Dr. ENDICOTT. One would, sir, but, as I explained, the Cancer Institute has not had a large demand for either fellowships or training.

Mr. DENTON. Would you want to put in the record how much more you would need to maintain the progress that you have made, to keep the program on an even keel?

Dr. ENDICOTT. Yes, sir.

(Information to be furnished follows:)

FELLOWSHIP NEEDS

To bring the NCI fellowship program up to the 1964 level, $144,000 would be required.

TRAINING GRANTS

Mr. DENTON. Training grants are going the same way. You are budgeting for 20 fewer training grants in 1965 than you are making in 1964. Do you have enough trained people in this field now?

Dr. ENDICOTT. No, sir; we do not have what I would regard as enough trained people. I think this is generally true in the whole field of medicine, there is a deliberate policy on the part of NIH, Public Health Service, and the Department, and I believe supported by the Congress, to double the number of trained men in the period of a decade, from 1960 to 1970.

I am confident that an appropriate share of them will end up in cancer research, but I suspect that they will be primarily trained by funds provided to other parts of the NIH.

Mr. DENTON. Why are you cutting this back?

Dr. ENDICOTT. Well, we are planning some rearrangement of the training grant program in the next year.

CHANGE IN PROGRAM

Mr. DENTON. You say here that the program in 1965 continues to undergo an almost revolutionary change within a relatively stable framework. What do you mean by that?

Dr. ENDICOTT. Let me explain that. We have two general types of training which are provided in the cancer training grant program. One is research training, oriented toward training of research people, and this is the area, as I have been explaining today, which is being carried more and more by the National Institute of General Medical Sciences.

Now, we have another responsibility under the Cancer Act, which is training for service.

Mr. DENTON. For what?

Dr. ENDICOTT. For service. The training of doctors, dentists, nurses, public health experts, for the diagnosis, prevention, and treatment of cancer. And we have, for a number of years, had a program essentially a formula grant program, in the medical schools, dental schools, and schools of osteopathy, for the purpose of upgrading the general level of ability to manage the cancer problem on the part of practicing physicians and dentists, and so on.

Now, we have been less and less satisfied with this program over the past few years, and carried out some intensive studies of it, and had a recommendation last summer from the National Advisory Cancer Council that we amend this program, that we discontinue the practice of the flat formula grant to the medical schools and dental schools, and schools of osteopathy, and that instead we let this be a competitive program aimed not at just supporting average training, but in encouraging improvement in training and extending it—and I think this is very important.

Mr. DENTON. Are you changing your two programs? You had one for service and one for research. Are you consolidating them?

Dr. ENDICOTT. No, we are shifting emphasis from the research training program, which is largely, as I say, being picked up by the Institute of General Medical Sciences, and we are concentrating more on improving the training in cancer of all physicians and dentists.

Mr. DENTON. Let me see if I have this right. You are shifting emphasis from research to service?

Dr. ENDICOTT. That is right, we are changing from training for research to training for service.

Mr. DENTON. That is all it is?

Dr. ENDICOTT. That is right.

Mr. DENTON. Why does it require 20 fewer training grants than you had before?

Dr. ENDICOTT. This is simply an estimate. We think probably there will be fewer institutions that will be participating, now that this will not be a formula grant program. I suspect some institutions will drop out.

COLLABORATIVE STUDIES

Mr. DENTON. All right. Now we come to your other increase, which is $3,010,000 for collaborative studies.

Now, most of this comes under the heading "carcinogenesis." That includes virus activities.

Tell us what you are doing now, and how you plan to expand that program.

Dr. Endicott. Well, this type of designation, collaborative research, represents a type of planned program in which the staff of the Institute, with the help of outside consultants and advisers, lays out a specific planned attack on a particular problem, attempts to identify the institutional or industrial concern, or concerns thought most likely to be able to do the best job for the least money, and then goes out and invites proposals, often on a competitive basis, and then supervises the work fairly closely during the course of the work.

DIFFERENCE BETWEEN GRANTS AND CONTRACTS

Mr. Denton. These are grants?

Dr. Endicott. No, sir; these are contracts.

Mr. Denton. What is the difference between a contract and a grant?

Dr. Endicott. Well, I suppose probably a lawyer could answer that better than I, but basically a grant is designed to support the work initiated by and thought up by the applicant. In our parlance, a contract is used to support programs which are developed by the Government and, in fact, you go out and buy an answer to a specific problem which you have defined.

CHEMOTHERAPY SCREENING ACTIVITIES

Mr. Fogarty. You also mentioned that the chemotherapy screening activities under this program have been substantially changed. Is there anything you would like to add to what you said about this when we were discussing research grants?

In that regard, I think I should call your attention to a speech that was made by Congressman Sibal of Connecticut, on November 11—it has just been brought to my attention. The heading of the speech was "Government and the New Science." On page 21544, he said:

> In our support of basic research, we must take care that research devoted to applications of known principles does not soak up funds and talent needed for basic research, which grows more costly every year. For example, in much basic research today, there are important events which must be measured occurring in a billionth or a one-hundredth of a billionth of a second at the subatomic level. Equipment needed to measure just one such event is enormously expensive.
>
> Yet, a survey of governmental programs in science today reveals a frequent misuse of funds on unnecessary programs at the expense of basic research.
>
> For example, there is a program sponsored by Federal money which will, in effect, test virtually any substance to see if it is effective against cancer. There is no selectivity. Anything sent in will be tested.
>
> By the end of this year, about $250 million will have been spent on this program. More than 170,000 compounds have been tested in what is one of the most unscientific approaches that can be imagined. Yet a willing Congress has provided the funds for it. The directors of the program admit that very little has come from the enormous effort. At the time it was initiated and subsequently up to today, scientists have deplored this type of shotgun approach and have pleaded for a more rational way. The program's defenders insist that it should continue, because by sheer happenstance, they may discover something useful against cancer.
>
> Perhaps so, we all certainly hope so, but we should also ask whether this enormous program has not drained off sums that would have been better applied to fundamental studies on the prevention and cure of this dread disease.

Mr. FOGARTY. Needless to say, I do not agree with Mr. Sibal at all.

Dr. SHANNON. Could I comment on that statement, Mr. Fogarty?

Mr. FOGARTY. Yes, sure.

JUSTIFICATION OF EMPIRICAL RESEARCH

Dr. SHANNON. In general, what is not commonly appreciated is that essentially all the drugs in use today were developed through an empirical approach—trial and error. This is true of antibiotics and a whole host of others.

Another source of new advances takes folklore as the starting point— for example the relation to the central nervous system of drugs derived from rauwolfia and the like. It is inadequate to approach the problem of therapeutics in a strictly logical fashion.

I think when we embarked on this cancer chemotherapy program, we did it with our eyes wide open. I think the testimony will show that year after year we said that we could not be completely certain that this was a profitable expenditure of funds in terms of what we would get, as the result of 5 or 10 year's effort; but, on the other hand, we felt that the disease was sufficiently important and that the promise of this approach was sufficiently great—by comparison with other possible types of activity—that the effort had to be made.

We pointed out that this type of activity did not tie up a large amount of scientific talent, so it would not in fact reduce other approaches to the disease. Therefore, if we had the funds, then we should certainly expend them for this purpose.

We also said that the day would come when this situation would have to be reassessed in order to determine whether we have gained enough to warrant a continuation of this type of activity or whether it should be modified. The first reassessment was made some 3 or 4 years ago. At that time, a quite marked reorientation of the screening program took place.

The program has been reassessed during the last 18 months in light of a great deal of new knowledge, and again it has been reorganized on the basis of the information available.

Mr. FOGARTY. But none of this has been done because of statements like this?

Dr. SHANNON. It has not been done because of statements such as that, no, sir. I think that the Congressman is just in error. I think he is misinformed.

Mr. FOGARTY. According to your statement, he is completely in error.

Dr. SHANNON. I will agree, sir.

I think there is a fairly substantial body of scientists in this country who really do not—well, approve of this type of approach, for precisely these reasons. There are many scientists in this country who would never undertake an industrial type of development, and this, of course, is an industrial aproach. This is the reason we have not felt that this area was suitable for grants, and the reason why we went to industry for the bulk of the work that was to be done. It is not an approach ideally suited to the inquiring type of mind that is characteristic of the academic environment.

So I think we find a certain built-in prejudice against this type of work, and the more fundamentally oriented the scientist, the more prejudiced he is.

I have heard from many scientists that one should not undertake a search for therapeutic agents of this general sort before one fully understands the mechanisms we are trying to interfere with. But I would say that if this were true, we would not have the antibiotics, nor the antihistaminics, nor the blood pressure agents, nor the tranquilizers. We would not have any of the drugs that are available today that have been developed by precisely those mechanisms that the Congressman deplores.

So, the gentleman is incorrect, sir.

Mr. FOGARTY. That is a good answer.

I wish you would supply for the record a statement in answer to any other criticisms of this program that have been made in the past year by congressional committees or scientists or voluntary organizations, or any other person or organization.

Dr. SHANNON. We will be glad to send it.

(The requested information follows:)

REPORT ON CRITICISMS OF CHEMOTHERAPY PROGRAM

The only specific criticism of the chemotherapy program during the past year of which we have any knowledge is the one made by Mr. Sibal which was quoted above.

SCREENING PROGRAM IN CHEMOTHERAPY

Mr. FOGARTY. Tell us about the screening program in chemotherapy.

Dr. ENDICOTT. There have been several changes. These have been underway for some time.

Mr. FOGARTY. Supply that for the record.

(The requested information follows:)

THE CANCER CHEMOTHERAPY PROGRAM AND ITS EVOLUTION

Objective.—To find chemical means for the management of cancer either alone or in combination with surgery and radiation.

Initiation of program.—At the request of Congress.

Modus operandi.—Combination of direct operations, contracts, and grants. Direct operations are concerned primarily with drug evaluation in the laboratory and clinic. Contracts support drug development and drug evaluation up to the clinical level. Grants support clinical trial (programed chemotherapy grants). From a dollar standpoint, direct operations represent approximately $2,673,000, contracts $25,495,000, and grants $5,400,000 for programed chemotherapy. In addition, regular research grants support a large number of independent or semi-independent chemotherapy research projects carried out in outside institutions; these total about $14 million.

EVOLUTION OF THE PROGRAM

In 1955 when the Cancer Chemotherapy National Service Center was established, there were a few different kinds of chemicals capable of producing temporary remissions in several different forms of cancer. These included alkylating agents such as nitrogen mustard with activity against lymphomas and leukemias, antivitamins such as aminopterin active against acute leukemia, antimetabolites such as 6-mecaptopurine active against acute leukemia, and hormones such as testosterone active against cancer of the breast and cortisone active against acute leukemia.

There was no known laboratory model system which was capable of predicting these activities and no model which would respond to all of them. A survey had recently been completed which showed that of the then known compounds active against human cancer, 95 percent would be detected by the use of a combination of three transplantable mouse tumor systems. After a study of the various available tumors from the standpoint of reproducibility, stability, and availability of inbred strains of mice, three tumors (sarcoma 180, leukemia L–1210, and carcinoma 755) were selected as the battery of tumors for the primary screen. It was proposed to operate this primary screen on a large scale and to accept chemicals from all over the world in an empirical search for new chemicals which might be active in man. It was also proposed to select those having the greatest activity, to carry out pharmacological studies on them, and for those passing the pharmacological tests, to undertake clinical trial in various forms of human cancer. It was recognized that the laboratory tests were incapable of predicting which, if any, human cancers might respond, but it was hoped that by correlation of clinical and laboratory data on various compounds selected for various tumors, some pattern or predictability might emerge. It was obvious at the outset that the arbitrary selection of the three tumors for the primary screen did not necessarily represent the best selection of tumors. Steps were taken immediately to explore in an orderly way a great variety of other test systems, including other transplantable tumors in various species, induced tumors, spontaneous tumors, tissue cultures, microbial cultures, and enzyme systems. It was also recognized that in addition to the empirical search, there should be an aggressive followup of potential rational approaches such as synthetics and testing of potential antimetabolites and synthetic steroids. It was also obvious that there would have to be pilot plants for batch synthesis, production contracts to obtain large numbers of uniform experimental animals, formulation laboratories to prepare materials for use in man, and a variety of other auxiliary services.

A survey of the distribution of different types of cancer and the frequency of their admission to given hospitals disclosed that no single hospital would see enough patients of a given type to complete a therapeutic trial in a reasonable period of time and that it would, therefore, be necessary to organize groups of hospitals, utilizing the same protocol and working simultaneously on the same drug. The logistics were further complicated by the fact that different types of cancer are treated by and controlled by different medical and surgical specialties. Hematologists treat leukemia; gynecologists treat ovarian tumors; urologists treat bladder tumors, etc. It was, therefore, decided to establish cooperative groups of hematologists, of gynecologists, and of urologists, etc., for the definitive trials in man. For the agents then available there were few, if any, reliable quantitative comparisons and it was felt that the collaborative groups could develop protocols and learn to work together by carrying out definitive studies of agents already shown to have activity in man, leaving for the time being the problem of organizing for clinical pharmacology and broad spectrum screening. From this beginning, the program began to develop some aspects more rapidly than others. The highlights are as follows:

Fiscal year 1956—first programed screening contracts; first pharmacology studies; first clinical studies groups; policy on submission of confidential compounds established; first contracts for developing better screening methods; first mouse breeding center established; and first submission of chemicals from industry.

Fiscal year 1957.—Congress earmarked funds for endocrinology; Endocrinology Panel established; first antibiotic beers screened; first interesting new compound found (NSC–1026; 1-aminocyclopentane carboxylic acid); first contracts for synthesizing compounds; first hormone assay contracts; and Contract Review Board established.

Fiscal year 1958.—Department of Health, Education, and Welfare amplified the patent policy applicable to cancer chemotherapy industrial research contracts; Authority given the National Institutes of Health for cost-reimbursement contracts; first industrial research contract; Contract Review Board superseded by Chemotherapy Review Board of Council; and first genetic mouse breeding centers established.

Firscal year 1959.—First industrial research contract for total drug development.

Fiscal year 1960.—First large overall program review by four ad hoc advisory committees. The committees recommended:

"1. That some mechanisms, such as executive committee, be instituted to provide a greater degree of overall central planning and coordination.

"2. That data-processing activities be extended to a greater extent to permit more effective and rapid evaluation, on a continuing basis, of the relationship of chemical, animal, and clinical data.

"3. That we clarify the confusion which exists in the minds of some regarding which proposals should be supported by research contracts and which by grants.

"4. That plants be explored more extensively as a source of agents with antitumor activity.

"5. That the clinical program provide for expansion of short-term evaluations, in a wide spectrum of human cancer, of all new types of agents with unequivocal antitumor activity in appropriate animal screening systems. These studies are to be in addition to the studies that have already been so effectively developed in those malignant diseases classified as responsive to chemotherapeutic agents.

"6. That clinical testing be expanded to accumlate, over a period of several years, quantitative data of the effect of presently known agents on a substantial number of types of human tumors. This data will be used to determine the degree and type of correlation that may or may not exist between drugs effectiveness as evidenced in screening systems and in human malignant disease."

Fiscal year 1961.—Regional groups established for broad spectrum testing in man; broadening of animal screen to include more than 20 different test systems; and orderly reduction in rate of screening under the 3-tumor system.

Fiscal year 1962.—Intensive review of correlation between clinical and laboratory findings, leading to establishment of leukemia task force.

Fiscal year 1963.—Outside advisory groups abolished; staff committees established and intensive total review initiated.

CURRENT STATUS OF THE PROGRAM

The current status of the program is presented below in greater detail in two sections, the first extracted from a report on contract activities of the Cancer Chemotherapy National Service Center, as prepared for the National Advisory Cancer Council, October 28, 1963, and the second extracted from a report on the clinical drug evaluation program (programed chemotherapy grants) as of February 1, 1964.

Highlights of Contract Activities in the Cancer Chemotherapy Drug Development Program Collaborative Research, CCNSC Area

CONTRACT ACTIVITIES

A major portion of the studies in man is funded through research grants to cooperating clinical groups. The remainder of the program is financed primarily under contract. These activities depend heavily on additional collaboration with the intramural functions of the National Cancer Institute, with research grantees, and with a number of major pharmaceutical companies. Programs under contracts have been developed in:

1. Compound synthesis.
2. Fermentation research.
3. Natural products collection and isolation.
4. Dosage formulation and quality control.
5. Screening and endocrine assay.
6. Experimental therapeutics.
7. Preclinical pharmacology.
8. Methods research.
9. Drug metabolism and drug action studies.
10. Biochemistry of human tumors in relationship to chemotherapy.
11. Radiation and host modifiers.
12. Animal procurement and disease control.
13. Material resources.
14. Clinical management activities.
15. Data processing, reporting, and analysis.
16. Statistical services.
17. Literature information, storage, and retrieval.

SUMMARY OF ACTIVITIES

During the past year the program has:

1. Procured and tested over 25,000 agents including—
    8,000 synthetics;
    12,000 fermentation products;
    5,000 plant extracts; and
    455 endocrine substances.
2. Procured or synthesized 37 agents for clinical trial.
3. Prepared adequate dosage forms with adequate quality control for 80 clinical agents resulting in almost 500 preparations.
4. Carried on approximately 160,000 primary in vivo screening and related tests in more than 20 test systems, and approximately 20,000 cell-culture tests.
5. Extended primary screening into a completely diversified screen of more than 20 different animal screens and several cell-cultural, microbial, and biochemical screens.
6. Carried out 6,500 hormone-assay and hormone-related tumor tests for selecting new endocrine agents.
7. Selected 25 agents for clinical trial.
8. Carried out preclinical pharmacology studies on approximately 50 compounds.
9. Studied over 40 new test systems; selected and established an acute leukemia-oriented screen.
10. Prepared and evaluated several hundred analogs of materials related to those in clinical trial.
11. Maintained an electronic data-processing system which processed raw data of over 250,000 experiments on animal screening, cell cuture, hormone assay, biochemical tests, alkaloid tests, etc., and produced summary data lines which were partially analyzed by computer into suitable reports for staff, suppliers of materials, clinicians, consultants, etc.
12. Produced and edited by data-processing equipment camera-ready copy for eight supplements to "Cancer Research" of summarized data on several thousand compounds. Of particular significance was the production of supplement XXI representing a monumental literature survey on screening systems by Dr. Erich Hirschberg.
13. Produced and edited by conventional techniques nine issues of "Cancer Chemotherapy Reports."
14. Prepared and published 12 issues of "Cancer Chemotherapy Abstracts" containing approximately 5,500 abstracts.
15. Produced or procured approximately 3 million experimental animals, mostly genetically inbred mice and rats.
16. Maintained a coordinated clinical program with 24 cooperating clinical groups and studied over 200 agents including about 50 new ones in over 10,000 patients.

IMPORTANT CONTRIBUTIONS TO SCIENCE GENERALLY

In the development of an extensive and comprehensive program of this magnitude, many major needs for resources, services, and other collateral activities, had to be met.

This resulted in a large number of accomplishments far beyond the specific scope of the chemotherapy program. These benefits have accrued to the entire scientific community. These include training of hundreds of scientists in cancer research including basic research; the development of a clinical research resource on a national level, trained in objective evaluation of new drugs, more sophisticated in the use of statistical and biomedical techniques, and capable of mounting a major clinical evaluation of new agents on a cooperative basis to produce meaningful clinical assessments in a brief period of time; synthesis of unusual chemicals for clinical trial and for basic studies of cell growth at a molecular level; anticancer drugs developed from this program are important to scientists studying DNA and RNA inhibition—some are potentially useful antiviral agents; provision of adequate resources and standards for high-quality experimental animals and facilities for the entire scientific community; establishing large-scale cell culture and animal tumor banks; establishing diagnostic centers for animal diseases which have all but eliminated ectromelia in the United States and reduced salmonellosis to the vanishing point; pioneering in the development of sophisticated data-processing systems, information storage and retrieval systems for biological research, etc.

CHANGES IN ACTIVITIES

Programmatic research such as that carried out in the collaborative research—CCNSC area needs to be dynamic and aggressive in order to progress. Any point in time (like the present report) does not necessarily reflect this. It is essential to review what existed prior to this period and where it will shift to in the future. Shifts do not occur easily or rapidly in programs of this size. Past experience indicates that it takes at least 2 years to effect a substantive shift in emphasis.

A few shifts in activities which have occurred during the past year are illustrated by a few examples taken from table I. Natural products development (item II) diminished by 0.3 million, or 10 percent. Fermentation research and related assay testing were reduced by 0.5 million, or 20 and 15 percent, respectively. However, production of natural products for pharmacology and clinical studies (item IIE) almost doubled, and plant isolation and related assays expanded greatly.

Drug evaluation activities (item III) dropped by 0.7 million (12 percent), most of it reflected by a marked drop in primary screening (0.6 million or 20 percent) of fermentation products.

These illustrative changes reflect shifts in emphasis which began more than 2 years ago and are expected to continue for some additional time. The drug procurement and screening effort is being adjusted to establish an adequate flow of agents into the clinic.

The trend in the "Research and development activities" has been directed to the application of more basic biological approaches to the problems in therapy. These include expanded studies of the mode of action of drugs, drug and steroid metabolism, biochemical studies of human tumors, combination therapy, radiation modifiers, host defense modifiers, steroid metabolism studies, etc.

Despite the fact that an excellent, reliable mass screening program has been developed which incorporates the most effective experimental designs, there is no doubt that many of the test systems used represent only improved empiricisms which must be used until better means for selecting agents can be devised. Continued commitments at a substantial level to aggressive research and development along the lines indicated are projected.

Indeed, it is apparent that major intellectual experimental and technological advances have occurred in biology at the molecular level. Many crucial questions can be posed and definitive answers obtained regarding ultimate structure and function of cells. There is little doubt in anyone's mind that we have crossed the threshold into a new dimension in biology.

Those programs in cancer which are targeted toward specific objectives, such as therapy, diagnosis, and etiology, should meet the challenge of this new dimension as vigorously as those investigators who are oriented to the basic problems of growth. Until we can find the means to cross this threshold with our targeted programs, we shall have to continue with many of the empirical approaches in use at the present time.

TABLE I.—*Analysis of contract activities in collaborative research—CCNSC*

Type of activity	Number of contracts	Annual level	Percent
Total	146	[1] $22,990,000	(100)
I. Drug procurement		4,729,000	(20.6)
A. Preparative laboratories: [2]			
1. Clinical	15	1,159,000	(5.0)
2. Experimental therapeutics	17	1,259,000	(5.5)
B. New synthesis:			
1. Steroids	5	151,000	(.7)
2. Nonsteroids	7	1,368,000	(6.0)
C. Quality control, dosage formulation, etc	6	792,000	(3.4)
II. Natural products development		3,241,000	(14.1)
A. Fermentation isolation	6	1,012,000	(4.4)
B. Plant product isolation	7	326,000	(1.4)
C. Related assay testing	14	1,403,000	(6.1)
D. Related research and development	4	140,000	(.6)
E. Production for pharmacology and clinic	4	360,000	(1.6)
III. Drug evaluation		4,734,000	(20.6)
A. Primary in vivo screening	10	1,743,000	(7.6)
B. In vitro screening	9	558,000	(2.4)
C. Experimental therapeutics	12	1,630,000	(7.1)
D. Pharmacology	7	803,000	(3.5)
IV. Endocrine evaluation		789,000	(3.4)
A. Endocrine assays	6	455,000	(2.0)
B. Endocrine related tumors	10	334,000	(1.5)
V. Clinical evaluation [3]	3	1,511,000	(6.6)
VI. Animal procurement and supporting services		2,079,000	(9.0)
A. Animal production	30	1,417,000	(6.2)
B. Disease control	6	218,000	(.9)
C. Trust stocks and genetic control	5	232,000	(1.0)
D. Tumor and cell culture banks	7	212,000	(.9)
VII. Research services		1,361,000	(5.9)
A. Data processing	1	474,000	(2.0)
B. Statistical services (clinical)	6	371,000	(1.6)
C. Literature, publication, and related activities	3	380,000	(1.7)
D. Clinical management	4	136,000	(.6)
VIII. Research and development		4,546,000	(19.8)
A. New screening methods:			
1. In vivo	15	1,080,000	(4.7)
2. In vitro	10	536,000	(2.3)
3. Host endocrinology	10	217,000	(.9)
4. Endocrine tumors	12	367,000	(1.6)
5. Viral tumor chemotherapy	7	742,000	(3.2)
6. Biochemical	2	170,000	(.7)
B. Mechanisms of action and resistance studies	14	867,000	(3.8)
C. Biochemistry of human tumors	4	511,000	(2.2)
D. Miscellaneous	2	56,000	(.2)

[1] Not included are $1,700,000, used for such ancillary purposes as direct purchases of clinical drugs, auditing costs, adjustments for overhead costs, overruns, cost-of-living increases, etc.

[2] Includes steroids.

[3] Additional funds of $6,500,000 funded through program grants for cooperative clinical studies.

CLINICAL DRUG EVALUATION PROGRAM

I. OBJECTIVES

The primary purpose of the clinical program in drug evaluation is to test in patients with cancer those materials selectively chosen by means of the systems, criteria, and rationale embodied within the preclinical CCNSC program. The primary objective is to develop better agents for the treatment of cancer.

II. INITIAL ORGANIZATION WITHIN THE CLINICAL PROGRAM

As described in the introductory material to the CCNSC program, in view of the success of specific chemotherapeutic materials in a few malignant diseases and because of the impetus supplied by congressional and advisory groups, the CCNSC program was established in 1955. It was determined at that time that the clinical portion of the program should be carried out by means of units made up of groups of investigators cooperating together. The individual members of these groups would be selected on the basis of interest, training, experience, and to a certain extent within a specific geographic area. Each cooperative group appointed a chairman to lead the group activities, to preside over meetings which were held at frequent intervals, and to maintain liaison with the CCNSC.

In the beginning, each individual member of a cooperative group was supported through grant funds. The proposed program of the group and the individual grant applications of each member were evaluated by a study section which, in turn, made recommendations to the National Advisory Cancer Council. As an advisory group to the CCNSC, the Clinical Studies Panel made up of well-known investigators in the area of clinical cancer research, was appointed. This was headed up by Dr. I. S. Ravdin. In 1959, in addition to its advisory capacity, the Clinical Studies Panel acquired the duties of study section for the review of grant applications in the chemotherapy program. Several committees of the panel were organized. An Experimental Design Committee was established to evaluate all protocols within the various cooperative groups prior to actual initiation of the studies. A New Agents Committee was formed which reviewed preclinical data on specific compounds, determined the adequacy of the data, made recommendations for further preclinical studies if necessary, and advised on the direction for the initial clinical trials. A Cooperative Studies Committee was organized, held meetings three times a year during which the various chairmen made reports on the progress of their individual group projects. Finally, a planning committee was organized to consider new programs and direction within the area of cancer chemotherapy.

III. MODUS OPERANDI

Each individual cooperative group has become an integral unit within the total clinical program. The various groups can be categorized into two broad divisions: (1) those groups which study new agents and consequently may evolve a variety of different types of investigation, and (2) those groups whose investigative efforts center around a single protocol which, in turn, dictates precisely their clinical activities. The former groups hold meetings at rather frequent intervals, discuss in detail the results of current studies, review with the CCNSC representatives available new agents for consideration, and plan further investigative efforts. The statistical units for each group handle, analyze, and prepare for review the data which are accumulated and provide advice on proper design of new studies. Individual drug studies, as well as other investigative efforts are in general carried on following a prearranged plan which enables each investigative institution to make the same approach and to carry on studies in a uniform manner in order to provide comparable results. In certain instances, headquarters units have been established to assist the chairman in his administrative responsibilities and these units are usually supported through contract. Each group maintains detailed minutes of their meetings which, in turn, are forwarded to the CCNSC for review and distribution to the members of the Clinical Studies Panel.

In addition, all the groups provide at regular intervals reports on their activities and the status of individual studies. For specific kinds of clinical investigations, the actual day-to-day flowsheets for registering of patient data are provided to the CCNSC. Members of the staff of the Clinical Branch of Collaborative Research maintain close liaison and have definite responsibilities to one or more of the cooperative groups. Each individual staff member follows closely the various studies and the progress of drug evaluations in those groups to which he is assigned. He attends all group meetings, assists in planning, and reviews with group members data on new compounds contemplated for initial investigation.

Through the efforts of specific staff members of the Clinical Branch, adequate supplies of drugs for study are maintained. By means of contracted facilities, chemotherapeutic materials are prepared in proper pharmaceutical dosage form to meet rigid specifications before clinical use, to be assured of both activity and for proper safety precautions. In accordance with the recent Food and Drug regulations relating to investigative compounds, the Clinical Research, Collaborative Research, maintains detailed files on all compounds. At the time a new agent is forwarded for clinical trials to a cooperative group, the compound is properly registered with the Food and Drug Administration and the total preclinical data provided in accordance with the law.

As indicated previously, in the beginning of the program all new agents were offered to the cooperative group chairman at the time of their meeting every 4 months. This procedure has now been changed and today new compounds of new chemical structure usually enter into studies restricted to a specific region of the country by collaboration between the cooperative groups within this region. Committees made up of members of each cooperative group in a region meet with representatives of the Clinical Branch of Collaborative Research and of CCNSC to review in detail data on new materials. Appropriate compounds are then studied within and between these groups, each group being responsible for a specific phase of the investigation. This arrangement will be discussed in more detail later.

As individual projects of the cooperative groups are completed, the members involved are urged to consider publication of data in Cancer Chemotherapy Reports so that prompt dissemination of the information can be assured. At the same time the total effort of all cooperative groups and the progress to date is published in outline form twice a year in Cancer Chemotherapy Reports.

Currently a central statistical unit has been established for the primary purpose of handling clinical data on new drug trials utilizing electronic data processing equipment. Onstudy cards have been designed for each patient entered into a study in addition to appropriate forms or flowsheets for the collection of day-to-day patient data. These items are forwarded by the individual investigators to their group statistical unit. Punchcards are made for computer use and these, along with the actual basic patient data, are forwarded to the central statistical unit for storage, retrieval, and analysis. The patient forms are used to evaluate the status of selected studies and to assist in further planning, as well as to make correlations with animal screening systems.

At the present time the Clinical Studies Panel reviews all grant applications for cooperative group effort. The Panel meets three times a year for 2 days each time. The first day is spent on program review of the various cooperative groups in turn and to advise on the direction of specific programs. The second day is then spent on reviewing individual grant requests. An Executive Committee of the Clinical Studies Panel has also been organized and currently meets at approximately 2-month intervals to review in detail problem areas, to consider program direction, and to assist the members of the Clinical Branch in an advisory capacity.

The Veterans' Administration participates also in the cooperative group trials as separate VA cooperative groups, although in a few, members of VA institutions participate in some university groups. Although the progress of the VA group is reviewed by the Clinical Studies Panel, the funds for support for the VA program are derived from contract money by means of direct transfer to the Veterans' Administration.

IV. EVOLUTION OF PROGRAM

As referred to previously, because of the established effectiveness of specific types of chemotherapeutic agents in a few malignant diseases, and due to the interest of advisory and congressional groups, the CCNSC and its cooperative group program were first established in 1955. Scientific rationale and impetus for this clinical effort originatel largely because of the effectiveness of certain classes of compounds; e.g., the antifolic acid compounds and the antipurines in acute leukemia, the alkylating agents in the treatment of chronic leukemias and Hodgkin's disease, and the hormonal agents in acute leukemia, breast and prostatic cancer. In a program founded to develop and evaluate new chemotherapeutic agents it was clear that no single institution would have a cancer population sufficient to evaluate compounds in a rapid and effective fashion. By using common protocols and uniform methods, it was felt that a group composed of investigators from several institutions would be able to study any single compound or method of treatment by cooperative efforts much more quickly and adequately. The cooperative group approach would not only provide a more rapid means of evaluation but, in addition, would supply adequate, comparable patient material to enable investigators to come to more satisfactory and scientific conclusions as to drug effectiveness on the basis of significant numbers. Not only should the uniform approach to drug studies be of distinct value, but also the cooperative group approach would lend itself well to the evaluation of methodology in clinical drug research. At the same time, within the individual cooperative groups, communications could be maintained at a high level and prompt dissemination of all types of clinical data, including drug toxicity and response, could effectively proceed.

As the cooperative group program evolved, various definitions for different types of clinical investigations were derived. All studies today are categorized as being one of three types:

Phase I is the initial study of a new drug in humans. Such a study involves the careful search for limiting toxicity, various essential aspects of clinical pharmacology, and, in addition, the determination of an adequate dosage schedule for investigative use.

Phase II studies utilize the dosage schedule derived in phase I in general, with provision for variation among individual patients in order to determine whether or not the compound has antitumor activity against one or more different types of malignancy. Since the beginning of the program, phase II studies have become essentially a screening device in the clinical evaluation of new agents.

Phase III studies in general are a detailed comparison between one agent and another or between methods of therapy in order to determine which is better. Such studies usually involve a large number of randomized patients and the experimental materials and the standard compound or placebo are double blinded.

When the program was started in 1955 there were essentially no new agents available for study. It was not until approximately 1959 and 1960 that the preclinical program of the CCNSC provided new compounds regularly for clinical trial. During this interim period, however, the cooperative groups already organized devoted the majority of their time and effort to comparing those agents currently in use when the program began. This was a valuable period for all cooperative groups and for clinical experimental therapeutic evaluation in cancer. Cooperative group investigators had an opportunity to study and evolve appropriate experimental design and standards for drug evaluation. Participants learned the significance of adequate statistical approaches and analysis. In addition, with relationship to the individual patients and types of cancer, investigators were able to study and determine what most appropriately could be utilized for assessing response. Criteria for selection of patients and for the determination of response were developed. Within the past 2 years a uniform protocol for phase II solid tumor studies and uniform reporting forms for all types of studies have been developed enabling comparison of results to be made from one group to another and allowing readily for joint efforts between groups. The common protocol and uniform forms permit computer processing and analysis of clinical data which in turn presents a much more ready assessment of results in the program.

V. CURRENT STATUS

Since the beginning of the CCNSC program, well over a hundred chemotherapeutic materials have been tested or have entered into clinical trials. The actual number of patients treated per agent may have varied from a very few to over several hundred, depending upon the nature of the study, the type of chemical compound, and the kind and intensity of the toxicity which may have been elicited. Included among the agents evaluated would be several which were in existence at the time the program began, and appropriate analogs developed through chemical synthesis. Over 55 materials have been hormonal, and tested primarily in advanced breast cancer patients.

Under the auspices of the clinical program have been tested materials developed within the activities of the CCNSC itself and also some materials obtained from outside sources. A few of the compounds tested have shown sufficient activity to warrant comment.

Methylglyoxal-bisguanyl hydrazone (Methyl-GAG) is the first chemical material to show a major degree of activity against acute myelocytic leukemia of adulthood. L-Sarcolysin has been found to produce objective response in patients with multiple myeloma, previously a very unresponsive disease to all modes of treatment. Preliminary indications suggest distinct prolongation in longevity. Cytoxan, an alkylating agent, has been proven to effect complete, though temporary, remission in acute leukemia of children. Vincristine, a plant extract developed by Eli Lilly & Co., will also produce complete remission in a high percent of children with acute lymphocytic leukemia; 5-Fluorouracil and 5-Fluorodeoxyuridine are the first agents to be in any degree effective against carcinoma of the colon. O,p-DDD is capable of reducing metastatic lesions of adrenal carcinoma, previously unresponsive to chemical agents, in a significant number of patients. Mithramycin, an antibiotic, has been found to produce obejective effects in some patients with embryonal carcinoma of the testis. One hormonal agent 2-alpha-methyl 4,5-dihydro testosterone has been found to be slightly better than the old standard testosterone in its ability to produce remissions in breast cancer, at the same time being less androgenic in its side effects.

To date over 30,000 patients have been entered into the various studies in the cooperative group programs. Approximately 900 clinical investigators participate in some type of drug trial. Around 250 hospitals are included in the program.

Within the scope of the clinical drug program, currently emphasis is being placed essentially in three areas. The first of these is a primary focus on phase I studies or on clinical pharmacology. Efforts will be made to establish specific units, backed by extensive laboratory assistance both directly for human studies with the best modern equipment and also preclinical animal laboratory facilities for pursuing various aspects or problems of drug distribution and metabolism which may arise during the course of investigation. These units will be capable of studying in depth the many types of agents which will be produced in the preclinical CCNSC program and will provide data which will be utilized in determining optimum dosage, route of administration, schedule, and limitation of serious toxicity.

The second area of emphasis is to foster the development of specific and total investigative programs in those diseases for which distinct chemotherapeutic leads have been derived. With greater focus, activity, and more coordinated effort on such diseases, it seems clear that more rapid progress can be made in defining preclinical systems which predict for these diseases, in arriving at better agents for therapy, and in determining optimum total care. To bring about this effort, collaborative arrangements will be made not only between the clinical investigators, but also between the clinical and preclinical investigators. To promote the necessary cooperation and emphasis, a member of each group studying the particular disease under investigation will be associated with the program. This sort of arrangement has already been carried out in the area of acute leukemia where an acute leukemia task force has been formed. As indicated, it is composed of specific members of the cooperative groups studying acute leukemia and, in addition, individuals from the preclinical area who have specific interest in those systems which appear to relate to selection of agents for clinical trial in acute leukemia. Considerable effort is being made in trying to work out appropriate screening tools for new agents to be tried in acute leukemia. At the same time, total therapy is under consideration and studies are carried out in the replacement of platelets and white blood cells to alleviate the problems of hemorrhage and infection and to promote a greater possibility of successful chemotherapy.

Three other types of diseases will be given this same sort of emphasis. The chronic leukemias, the lymphomas, and breast cancer will receive added attention from the standpoint of total therapy, predicting systems, and appropriate studies. Again, efforts will be made to coordinate the present evaluations being conducted in cooperative groups by selecting specific members from those groups studying these diseases. Where appropriate, consideration will be given to other modalities of therapy which might require further emphasis; e.g., radiotherapy.

The other area in which emphasis will continue to be placed is in the development of leads in those diseases for which at present chemotherapy offers no benefit. Broad spectrum screening by means of phase II studies in the more frequent types of malignancies, predominantly solid tumors, will continue. Wherever distinct leads may develop, correlations will be made with preclinical predicting systems, further intensive screening will be directed, and systematic efforts made to develop those chemical classes of compounds which show activity.

At the present time, in order to carry out broad spectrum trials and to allocate properly new agents for the types of testing necessary, a regional approach in distribution has been set up. The country has been divided into three regional areas and a fourth is constituted by the Veterans' Administration. Within each region are both hematologic and solid tumor groups. Committees have been organized for each region to evaluate new agents and to organize appropriate phase I studies in those groups which carry out this activity. Once a compound is ready for phase II investigation, within each region, the hematologic groups study it in the various hematologic malignancies and the solid tumor groups conduce phase II investigations in selected solid tumors. In this way broad spectrum studies with any single agent can be facilitated. New agents for phase I and II studies are consequently restricted to a single region to avoid reduplication of effort.

MAMMOGRAPHY

Mr. FOGARTY. The long-range study to determine the value of mammography, which you mentioned on page 115—you have talked about this?

Dr. ENDICOTT. Yes.

Mr. FOGARTY. The people in the Chronic Disease Division seem to think much more of this as a diagostic tool than you do, if I remember correctly what they said.

Dr. ENDICOTT. But not as a population screen.

Mr. FOGARTY. No, as a diagnostic tool.

Dr. ENDICOTT. We are agreed.

It is a very useful diagnostic aid, but not as a primary screen.

Mr. FOGARTY. But it is a way of determining breast cancer, one that cannot be palpated—is that the expression they used?

Dr. ENDICOTT. Yes. This means to feel the cancer by the sense of touch.

GHANA LABORATORY

Mr. FOGARTY. You are requesting $111,000 for rotation of the staff who have been at the Ghana laboratory for a period of 2 years. How many Americans are stationed at that laboratory?

Dr. ENDICOTT. I believe the figure at the moment is 24.

Mr. FOGARTY. Will you supply for the record a statement about the activities carried out there, the plans for the future, how you are getting along with the Government, and how much they contribute?

Dr. ENDICOTT. Yes, sir.

(The requested information follows:)

SPECIAL REPORT—GHANA

The National Institutes of Health-National Institute of Health and Medical Research joint research program—Ghana (formerly the NIH-West Africa Research Laboratory—Ghana) was established in 1962 in response to a request from President Nkrumah of Ghana to President Kennedy of the United States. President Nkrumah asked that the U.S. Government collaborate with the National Institute of Health and Medical Research of Ghana in developing a program of medical research on health problems of concern to both countries. Under a formal agreement the Ghanaian Government provides laboratory and clinical space, facilities, and housing; the U.S. Government provides professional and technical staff, equipment, and supplies.

There are 24 Americans and 46 Ghanaians on the staff in Ghana. Dr. John H. Edgcomb, formerly of the National Cancer Institute's Laboratory of Pathology, was appointed U.S. officer in charge. Although specific administration of the Ghana Laboratory was delegated to the National Cancer Institute, it was organized to enlist the aid of all interested institutes of NIH in the study of major disease problems affecting the population of West Africa as well as of the United States.

The staff has seen a wide spectrum of tropical disease in Ghana, chiefly at the Korle Bu Hospital and the James Town Clinic in the heart of Accra, but also in the rural areas. Ghana offers many unusual opportunities for the study of diseases in advanced stages which are rarely seen in unmodified form in the United States. The country also presents a cross section of the cancer problems in Africa south of the Sahara and is in the region which apparently has a high incidence of an unusual lymphoma (a tumor).

Excellent housing and some laboratory space have been provided by the Government of Ghana. Well-equipped modern laboratories have been established, and a unit for clinical investigation has been activated. These are served by a strong administrative staff. With such facilities available as a base, it is now possible to develop highly sophisticated programs in almost any area of research on diseases in Ghana.

High priority has been assigned to studies of the parasitic diseases, schistosomiasis, filariasis, and especially onchoceriasis, as well as of hepatitis, and inflammation of the liver. Schistosomiasis, a parasitic disease involving a common fresh water snail as an intermediate host, is a major disease problem in Ghana, and is expected to become even more prevalent after completion of the Volta River Dam, which will introduce widespread irrigation in previously arid areas.

Following the worst floods in the recorded history of Ghana, which isolated the northern part of the country in the fall, severe jaundice with high mortality was reported in the Damongo area. This raised the question of a possible outbreak of yellow fever in addition to a high endemic rate of infectious hepatitis. (Both diseases produce similar symptoms although mortality is usually higher in yellow fever.) The NIH–NIHMR was instrumental in diagnosing yellow fever in some of these cases, based on studies carried out by our unit in Ghana and confirmed by the Armed Forces Institute of Pathology and by the Communicable Disease Center in Atlanta. There seems little doubt that some yellow fever has been occurring in the midst of a high regional incidence of infectious hepatitis. The Entomology Section is now engaged in a survey of the Damongo area for the transmitting mosquito, *Aedes aegypti.*

A program of coordinated clinical investigation has been set up to study pulmonary disease among children in Ghana. Major emphasis is placed on tuberculosis, but nontuberculous pulmonary diseases will also be included. Involved in this study are the tuberculosis pediatric wards in the Princess Marie Louise Hospital and the Korle Bu Hospital, and the tuberculosis clinic in James Town. This is a long-range project with focal points for the organization of (1) a pediatric chest clinic to be physically located in the Korle Bu Hospital; (2) a tuberculosis and chest clinic in James Town; and (3) a small laboratory at the Korle Bu Hospital.

The NIH–NIHMR has been asked to participate in the malaria eradication program for the greater Accra area, and to organize and train the Ghanaian personnel for participation in a pilot study of malaria eradication in the James Town section. Plans are also under discussion to try new antimalarial drugs in Ghana. Our chief entomologist has been requested to act as head of the vector-borne disease unit for the entire Volta River area.

There is considerable urgency in introducing a measles vaccine program in Ghana since measles is a very serious disease in this and some other tropical countries. The present measles death rate among Ghanaian children is over 30 percent. During the past year, a pilot study was carried out on about 600 children in the village of Tsito to evaluate a measles vaccine that produced good immunity in the United States with minimal side reactions. This study had to be interrupted because of difficulties in vaccine production, but as soon as new lots of vaccine become available, it is anticipated that further studies will be carried out.

About 800 autopsies have been performed under the NIH–NIHMR joint research program, approximately half of them by the U.S. group. This provides the most extensive series of carefully executed autopsies ever carried out in Ghana, and is yielding accurate information for the first time about disease patterns and causes of death in that country.

In accordance with the developing concept of its mission, the NIH–NIHMR joint research program—Ghana is now in the process of reorganization. The staff will be oriented more by disease problems than by disciplines and a team approach will be employed in a well-coordinated interdisciplinary attack on certain important diseases of Ghana. New staff members will be recruited for specific roles in relation to these disease problems. However, no major expansion is contemplated.

OTHER SERVICES

Mr. Fogarty. I notice $2.69 million, or over half of the total increase, is in the object classification "Other services"; what accounts for this?

Mr. Kelly. That is contracts.

Mr. Fogarty. Contracts? Is that all contracts, Doctor?

Dr. Endicott. Yes.

Mr. Kelly. This is where the chemotherapy program shows up.

STATUS OF PLANS FOR RESEARCH FACILITY

Mr. Fogarty. You are asking that funds appropriated in 1961, for plans and specifications for a research facility be continued available until June 30, 1965. How many times have you asked for an extension of their availability?

Dr. Endicott. I think this is the third time, is it not, Mr. Kelly? Or the second? The third time, I guess.

Mr. Fogarty. What is the holdup on this thing? It seems to me it should have been built by this time.

Dr. Endicott. Yes; this has been very slow.

Mr. Fogarty. What is the problem?

Dr. Endicott. There have been a whole series of them, sir. I think perhaps I am not best suited to answer this problem, because the holdups have occurred at various other places.

In the first place, there are two buildings involved in the same complex. There is the same architect, there has been the problem of resolving eating facilities for these two buildings, which is in still a third building. Changes in one building necessitated changes in another. And of course there is a fairly elaborate system of clearances for the changes. The complexities of building the three buildings together with separate appropriations, and so on, has just made this an inordinately slow affair.

Oh, Mr. Learmouth whispered in my ear that I should mention when we completed our part of the planning. The preliminaries were provided by the Cancer Institute in November of 1960. So the basic program requirements, which is our part of the problem, have been available for quite a long time.

PAPER BY J. SPENCER MONROE AND WILLIAM F. WENDEL

Mr. Fogarty. I have a paper here by J. Spencer Monroe and William F. Wendel, "Tumors induced in primates by chicken sarcoma virus." Is this the first time this has been done?

Dr. Endicott. In primates; yes, sir.

Mr. Fogarty. Is this the same Dr. Wendel who was in charge of the program in neurology in Puerto Rico?

Dr. Endicott. Yes, sir; that is the same man.

Dr. Shannon. Yes.

Mr. Fogarty. What do you think about it?

Dr. Endicott. I think it is a very fine piece of work.

Mr. Fogarty. This shows some progress, then; does it not?

Dr. Endicott. Well, this is another example of manipulating a vrius until you can get it to cross species barriers. This same virus by other investigators has been shown to produce tumors, for example, in rats.

We have had similar experience with leukemia viruses, which were isolated first from mice, and then, after laboratory manipulation, would go in rats. The same has been true in polyoma. I think this is another example of manipulations which result in a crossing of species barriers.

PROFESSOR SEVERI

Mr. Fogarty. I talked to a Professor Severi from Perugia when he was here. Did you see him when he was here a few weeks ago?

Dr. Endicott. No, sir; I did not.

Mr. Fogarty. He was out at the Institutes a few times. He had a grant from you people. He was working on leukemia at the Cancer Institute in Perugia. Are you familiar with it?

Dr. Endicott. Yes, sir; I am familiar with the Institute, but I did not see him on his visit.

Dr. Lucio Severi is a distinguished medical scientist in Italy. He is director of the division of cancer research from 1953, dean of the Medical School at the University of Perugia from 1957, member of the World Health Organization Expert Advisory Panel on cancer, member of the committee of the Italian Cancer Society, affiliate member of the Royal Society of Medicine of London, and editor of "Lav.-Anat.Pat. Perugia." He has done sound work in oncology and has arranged a number of conferences of world leaders in cancer research. He has been a grantee of the National Cancer Institute but his support will soon be discontinued because of a national policy which is sharply limiting funding of research in Western Europe.

Mr. Fogarty. Is there anything else you would like to say about your activities?

PRESENT STATUS OF CANCER RESEARCH

Dr. Shannon. Before you close out the hearings, I would like to talk about something that came up earlier.

In listening to Dr. Endicott's testimony in terms of what has happened during the past year, I think the record, as you noted, will not be one to generate enthusiasm. I would point out, however, that the record limited to specific therapeutic gains against cancer doesn't really reflect the significance of certain encouraging things that have happened during the past year. We are coming into a phase of cancer research now where a great many quick gains have already been made, and we are settling down now for the really long haul. If one looks toward the future, toward fundamental solutions, and then notes certain gains—for example, in our understanding of the biology of cells and viruses—then we recognize that there have been broad and very significant advances that are quite beyond what we had envisioned.

Dr. Shannon. I think the increasing association of viruses or virus-like particles with leukemia in humans; the rapidly expanding knowledge of the cell's incorporation of virus as part of the nuclear material, with capacity for delayed action; the carcinogenic properties of certain adenoviruses from humans when introduced into suitable animal preparations—this whole area is beginning to be broadly clarified.

Mr. Fogarty. Before I go up and answer this quorum call, Mr. Denton has some more questions, and we will reconvene at 2 o'clock after Mr. Denton gets through.

Mr. Denton?

UNOBLIGATED BALANCE

Mr. DENTON. I notice that you have an unprogramed reserve of $7,341,000. Now, how much of that will you obligate before the end of the fiscal year, and when will you obligate it?

Dr. ENDICOTT. Yes. We will obligate it all, sir.

Mr. DENTON. You have projects ready to obligate it all?

Dr. ENDICOTT. Yes, sir.

Mr. DENTON. Why have you been so late in obligating it?

Dr. ENDICOTT. Well, sir, I think we are approximately on schedule in obligation, so far as I am aware. There has been some delay. The only delay I am aware of in obligation relates to the November meeting of the Council. At that time I was quite uncertain as to the availability of funds for the research grants, and postponed the payment of all grants below the very top priorities until I could find out.

Mr. DENTON. How do you rate them? How do you rate them, A, B, C, or what?

Dr. ENDICOTT. The applications that are reviewed by study section members and recommended for approval are rated by each member as follows:

(1) Excellent;
(2) Very good;
(3) Good;
(4) Fair;
(5) Acceptable; and
Abstention (for an individual who has reason not to vote).

The individual ratings are added, multiplied by 100, and averaged to provide three-digit ratings. The scores from all study sections are interdigitated into separate master lists of each Institute. Councils may recommend changes in the order of projects on the basis of consideration other than scientific merit; however, these ratings serve as the chief guide in determining which of the approved applictations will be supported financially.

Mr. DENTON. You would not go lower, four or five?

Dr. ENDICOTT. I cannot be sure, but I think we probably—as best I can tell at this point in time, we will probably be able to pay through the sixth decile; in other words, the top 60 percent of the grants.

Mr. DENTON. All right, that will be one, two, and three—or just one? Or what?

Dr. SHANNON. One, two, and three.

Dr. ENDICOTT. There will be some of each.

Mr. DENTON. So 60 percent will be one, two, and three, and 40 percent will be four and five? Is that right?

Dr. ENDICOTT. Roughly. I think the cutoff is around 270.

NOTE.—The 60 percent of grants to be paid refers to competing grants at the November 1963 and March 1964 council meetings. All grants acted on at the June council meeting have been paid.

VIRUSES

Mr. DENTON. On page 161 of your justification you tell about some of the human viruses found to produce tumors in hamsters, and you studied the blood and found there are antibodies, but do not find any virus.

Can you tell us anything more about that? That interests me.

Dr. ENDICOTT. Well, it interests us, too, particularly with cancer viruses. But this is true of some others as well.

A virus becomes undetectable or undemonstrable in the cell, oftentimes when the disease that is produced is at its height. One may find antibiotics with the virus no longer apparent, and then at some subsequent date, the virus may become apparent again as a result of some manipulation.

It is generally suspected that what really happens is that the virus is present but in a masked form, perhaps an incomplete virus. And it may very well be that it is, at that point in time, more or less hidden in the nucleus of the cell.

Mr. DENTON. Let me ask you, when there is a virus, do you always find antibodies?

Dr. ENDICOTT. No, sir. With any virus infection, there is always a period of some delay before antibodies appear. Usually 1 or 2 weeks before antibodies develop. They may persist for variable lengths of time, for life in some instances, just to a short time in others.

Mr. DENTON. When I went down to the Communicable Disease Center, I think I saw every disease organism in the world. They had them under microscopes. I thought if it was a virus, you would find antibodies and vice versa.

Dr. ENDICOTT. No, sir. Some cancer viruses are extremely poor antigens, and in some instances we have not been able to demonstrate an antibody of any sort, although we can demonstrate the virus.

Mr. DENTON. Now, what is a virus helper? You spoke of a virus helper. What is that?

Dr. ENDICOTT. This is simply another virus which apparently assists the first virus in producing the disease effect. It relates to its ability to synthesize a protein coat.

PRODUCTION OF CARCINOGENS BY OXIDATION

Mr. DENTON. Mr. Fogarty talked to you about burned things. Do burned things cause cancer, or what is it?

Dr. ENDICOTT. In the process of combustion, chemicals which are not carcinogenic are converted to chemicals which are carcinogenic, as a result of heat and oxidation.

Mr. DENTON. What do you mean by "carcinogenic"?

Dr. ENDICOTT. Cancer producing.

Mr. DENTON. Burned things do produce cancer, then?

Dr. ENDICOTT. Yes. In many instances this is true.

Mr. DENTON. Then a person had better not eat charcoal steak, if that is the case, charcoal-broiled steak, or burned potatoes?

Dr. ENDICOTT. Some might draw that conclusion. I am not prepared to go that far yet.

KREBIOZEN

Mr. DENTON. We are going to be asked about Krebiozen. Do you have any opinion on that?

Dr. ENDICOTT. Yes, sir, I definitely do have an opinion on that. Perhaps you would permit me to provide a report for the record.

Mr. DENTON. Yes, do that.

(The information supplied follows:)

STATEMENT ON KREBIOZEN

On September 29, 1961, Dr. Ivy and Dr. Durovic submitted to NCI a report on Krebiozen and their clinical experience in some 4,000 cases of cancer treated with Krebiozen. Two small samples of Krebiozen and two infrared spectrograms were also submitted. NCI accepted these items for study in order to determine whether to conduct or sponsor a clinical trial of Krebiozen.

On March 7, 1962, NCI wrote to Dr. Ivy and Dr. Durovic detailing the inadequacies in the September 29, 1961, submission and stating that the material did not justify clinical trial. Additional information was requested regarding the manufacture and laboratory testing of Krebiozen and the original case records on two series of patients.

On July 17, 1962, Dr. Ivy and Dr. Durovic wrote that they could not supply the original case records and suggested that NCI obtain the assistance of other Federal agencies having power to subpena the records.

NCI sought the assistance of FDA and Division of Biological Standards in obtaining the case records and further data on the manufacture and laboratory testing of Krebiozen. These agencies agreed to seek the necessary data in connection with their investigation of charges that Krebiozen was being sold in interstate commerce.

In August 1963, FDA supplied NCI with case records on 504 patients selected by Dr. Durovic to establish the effectiveness of Krebiozen. The records included copies of Dr. Durovic's records supplemented with hospital records, X-rays, microscopic slides, physicians' records and interviews of patient, physicians, and relatives.

NCI appointed a committee of distinguished physicians to review these records and recommend whether or not NCI should sponsor a clinical trial.

On October 15, 1963, NCI made public the committee's report which concluded that Krebiozen does not possess any anticancer activity in man and recommended that no clinical trial be undertaken.

NCI has accepted the findings and recommendations and regards the case as closed from a scientific standpoint.

Mr. DENTON. We will reconvene at 2 o'clock.

WEDNESDAY, FEBRUARY 26, 1964.

NATIONAL INSTITUTE OF MENTAL HEALTH

WITNESSES

DR. R. H. FELIX, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. STANLEY F. YOLLES, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

GEORGE A. VAN STADEN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF MENTAL HEALTH

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Object classification

[In thousands of dollars]

		1963 actual	1964 estimate	1965 estimate
	PUBLIC HEALTH SERVICE			
11	Personnel compensation:			
	Permanent positions	6,745	8,692	9,349
	Positions other than permanent	938	961	961
	Other personnel compensation	134	184	162
	Total personnel compensation	7,817	9,837	10,472
12	Personnel benefits	812	1,201	1,243
21	Travel and transportation of persons	799	884	930
22	Transportation of things	70	41	47
23	Rent, communications, and utilities	217	180	180
24	Printing and reproduction	123	116	134
25	Other services	3,777	4,302	4,059
	Payment to National Institutes of Health management fund	5,578	5,955	6,200
26	Supplies and materials	549	529	545
31	Equipment	488	411	472
32	Lands and structures	2	----------	----------
41	Grants, subsidies, and contributions	119,174	149,916	164,515
	Total, Public Health Service	139,406	173,372	188,797
	ALLOCATION TO ST. ELIZABETHS HOSPITAL			
11	Personnel compensation:			
	Permanent positions	77	75	75
	Positions other than permanent	1	1	1
	Other personnel compensation	4	4	4
	Total personnel compensation	82	80	80
12	Personnel benefits	6	6	6
23	Rent, communications, and utilities	22	28	28
25	Other services	----------	2	2
26	Supplies and materials	1	4	4
	Total, St. Elizabeths Hospital	111	120	120
	Total obligations	139,517	173,492	188,917

Personnel summary

	1963 actual	1964 estimate	1965 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions	958	1,214	1,253
Full-time equivalent of other positions	124	121	122
Average number of all employees	1,005	1,194	1,244
Employees in permanent positions, end of year	958	1,200	1,239
Employees in other positions, end of year	195	65	73
Average GS grade	7.8	8.2	8.2
Average GS salary	$7,290	$7,971	$7,937
ALLOCATION TO ST. ELIZABETHS HOSPITAL			
Total number of permanent positions	14	14	14
Average number of all employees	14	14	14
Employees in permanent positions, end of year	14	14	14
Employees in other positions, end of year	0	0	0
Average GS grade	4.8	4.8	4.8
Average GS salary	$5,148	$5,292	$5,292
Average salary of ungraded positions	$6,182	$6,182	$6,182

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	53,303	66,010	76,495
(*b*) Fellowships	5,940	7,788	8,057
(*c*) Training	49,117	65,168	73,213
(*d*) State control programs	10,814	10,950	6,750
Total, grants	119,174	149,916	164,515
2. Direct operations:			
(*a*) Research	10,203	10,755	11,203
(*b*) Collaborative studies	2,329	3,979	3,986
(*c*) Training activities	542	1,054	1,088
(*d*) Professional and technical assistance	2,823	3,982	4,224
(*e*) Review and approval of grants	2,773	3,181	3,264
(*f*) Program direction	590	625	637
Total, direct operations	19,260	23,576	24,402
Total program costs funded [1]	138,434	173,492	188,917
Change in selected resources [2]	1,083		
Total obligations	139,517	173,492	188,917
Financing:			
Comparative transfers to other accounts	396		
Unobligated balance lapsing	3,665	2,673	
New obligational authority	143,578	176,165	188,917
New obligational authority:			
Appropriation	143,599	183,288	188,917
Transferred to—			
"Operating expenses, Public Buildings Service," General Services Administration (76 Stat. 728 and 77 Stat. 436)	−21	−194	
"Salaries and expenses, Office of the Surgeon General" (42 U.S.C. 226)		−15	
"National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−6,914	
Appropriation (adjusted)	143,578	176,165	188,917

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[1] Includes capital outlay as follows: 1963, $741,000; 1964, $411,000; 1965, $469,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $1,802,000 (1963 adjustments, −$12,000); 1963, $2,873,000; 1964, $2,873,000; 1965, $2,873,000.

Mr. FOGARTY. The committee will come to order.

We have before us this afternoon the justifications for the National Institute of Mental Health.

General Statement

Dr. Felix, you have a statement for the committee?

Dr. Felix. Mr. Chairman and gentlemen of the committee, I have a prepared statement which has been filed with the committee.

(The statement referred to follows:)

Mr. Chairman and members of the committee, for two decades—minus only 1 year—it has been both my responsibility and my privilege to report to you on mental health activities in the Public Health Service and across the Nation. Among you who are so constructively interested in mental health problems, there are some who were present in 1946 when the National Mental Health Act authorizing the establishment of the National Institute of Mental Health was enacted.

Though the act was passed too late in that congressional year to permit the appropriation of funds to implement it, the following year I was able to report that the programs of the NIMH were underway. A private foundation had, in response to my request, contributed the funds which enabled us to begin.

As my annual reports to you since then have indicated, we have progressed far. I have been able to report that in the Nation's laboratories, training institutions, medical facilities, and communities many advances have occurred which have served to lighten the tragic burden of mental illness. We have made progress. We have increased by almost 400 percent the number of psychiatric outpatient clinics in the country. The number of trained professionals functioning in the mental health field has increased almost twice as rapidly as has the total number of health professionals. Today there are 56 fewer persons per 100,000 population in our public mental hospitals than there were in 1950. Though we cannot yet prevent the major psychoses, we can reduce the disabilities that have, in the past, accompanied the major mental illnesses.

Underlying all that I have reported to you in recent years has been the steadily recurring theme of decreased despair and of increased hope.

Scarcely a year ago this theme reached its crescendo in President Kennedy's remarkable message to the Congress and to the country on mental illness and mental retardation. The new attack on mental illness which he called for then, which has already resulted in new and far-reaching legislation, and which President Johnson mentioned as one of the great legacies left to us by President Kennedy, may indeed, as a recent editorial in the Washington Post stated, "prove to be one of the most significant events of this era." For, as the President said then, "we cannot afford to postpone any longer a reversal in our approach to mental affliction * * * reliance on the cold mercy of custodial isolation (must) be supplanted by the open warmth of community concern and capability. Emphasis on prevention, treatment, and rehabilitation (must) be substituted for a desultory interest in confining patients in an institution to wither away."

The events of the past year, Mr. Chairman, and gentlemen, have marked our emergence from an era in the history of our care of the mentally ill. Today the frontier of community psychiatry has been won. We are in transition from an era of primarily custodial care for many of our mentally ill to an era of treatment that is comprehensive both at any particular point in the patient's illness, and over whatever period of time—whether short, continuous, or intermittent—such treatment is needed.

We are now concerned with a framework of service which admits to no separation of prevention, treatment, and rehabilitation. This is the crux of the new concept of community medicine which focuses on the social functions of medicine as well as on the specific actions intended to prevent or cure disease in the individual patient. It implies that all organized services in the mental health field are mutually dependent one upon the other, and that care in any one setting—the home, the private practitioner's office, the public clinic, the hospital, or other institutions—is not isolated.

Further, this integrated approach to mental health problems we are now developing has a significance that reaches far beyond the confines of a treatment center. For the expansion of any community function requires and induces an advance in all others, and lack of progress in one community function holds back the whole community. One need only reflect for a moment on what may happen to the child who is severely and persistently psychosocially deprived to understand the truth of the preceding statement. Whatever facet or symptom or distress flourishes in a particular child as a result of the psychosocial stress he undergoes, any or all community institutions and agencies may be needed to relieve the child. For the job to be done is one community job for one psychobiologic unit—the child; not one mental health job, or one medical job, or one education job, or one welfare job.

The concept was stated more eloquently, many years ago, by Dr. Adolf Meyer, the late great psychiatric teacher. Dr. Meyer, whose system of thought has been called commonsense psychiatry, believed that the domain of psychiatry is the behavior of the entire man as he reacts to the stresses of his environment. In 1930, reminiscing about his work in a State mental institution in 1904, he recalled:

"I had to reach out, in my actual work, more and more toward a broader understanding of the patients, which led me to a study of the family settings and by and by also of the place where the individual first became a member of the community. The school * * * the life of the patient and of the family, the life of the patient in hospital, and the return to the community began to receive more practical attention * * *.

"Communities have to learn," he continued, "what they produce in the way of medical problems and waste of human opportunities, and with such knowledge they will rise from mere charity and mere mending, or hasty propaganda, to a well-balanced early care, prevention and general gain of health, efficiency, and happiness."

Mr. Chairman, the new approach outlined in President Kennedy's stirring call to action has given the Nation a long-awaited chance to "rise from mere charity and mere mending."

I have much to report to you concerning the work of the Institute during the past year to develop the new national mental health programs and to strengthen our already well established efforts. But since none of our work is meaningful unless it is related in some way to the everyday life of our people as they go about the business of living, I would like, at this point, to ask you to look with me at a small hypothetical cross section of a community.

A HYPOTHETICAL NEIGHBORHOOD

Let us try to imagine, then, what the lives and the mental health problems of a group of 100 persons living on the same residential block would be like. If these 100 persons were a characteristic sample of our entire population, and we thought of them as living in one block, then from the standpoint of the Nation's mental health concerns we can hazard the following characterization of this hypothetical tiny American microcosm:

It contains about 31 children and adolescents, plus 7 young unmarried adults—4 men and 3 women—who are in the labor pool, in the armed services, or continuing their education. There are 23 married couples, 1 widower and at least 4 widows. In every block lives a divorced man, and in every block a divorced or separated woman—who is quite likely to be under 45, and the mother of one or more children. There is one chance out of two that she will be obliged to work away from home to support her children.

In 1 out of every 3 such blocks this year some youngster in the 10- to 17-year-old group appears before a juvenile court on a delinquency charge; and of every three young men screened for service to their country, one is found unfit. In every block there lives at least 1 alcoholic; in every 40 blocks, at least 1 drug addict.

Every block will have 10 or more residents more than 65 years of age, many of them living alone and finding it progressively more difficult to get along in the fast-paced ever-changing world around them. This is the age group with the highest suicide rate in the Nation.

In the course of a year, many families and many individuals will face new and frequently difficult adjustments of living.

If this hypothetical block represents a true economic and social cross section, at least one-fifth of these families will be living in poverty, and some will be living in affluence. Not only will their economic status differ: they will have come from differing racial and cultural backgrounds, and these factors will have a bearing on their mental health.

Finally, in one out of every five such blocks each year some adult is admitted to a mental hospital for the first time, and two persons in every five blocks spends some time in a mental hospital. In all, it is estimated that approximately 10 persons in each such block need some form of treatment, care, or rehabilitation. Yet, given our present overcrowded facilities, the outpatient clinics across our land are able to see only one child in every nine blocks and one adult in every six blocks.

In studying this tiny hypothetical microcosm it becomes obvious that the mental health problem is not localized just in large State mental hospitals far out in the countryside, miles away from cities. Its place is at the very heart of every community. It is here that the problems of aging and the tragedy of mental illness are of immediate personal concern to families and relatives and friends and neighbors, to schools and churches and police and social agencies. Furthermore, in some areas where poverty and ill health and social disorganization form a fateful and intertwined trio, mental illness, alcoholism, drug addiction, suicide, juvenile delinquency, mental retardation and other social-medical problems are greatly magnified and reinforce each other.

As urgent as our mental health problems seem today, when viewed in this microcosm, they seem even more serious when we predict what our needs will be in 1980. In that year it is expected that our population will have increased from our current 189 million to somewhere between 240 and 260 million, thereby creating a potential for thousands of new neighborhoods or greatly increasing the population in each old neighborhood.

It is against this background that the new national mental health program called for in the President's message last year assumes its true significance. He proposed that we develop the mental health resources we need now and will need in the future. He urged: (1) the development of comprehensive community mental health centers; (2) the upgrading of the quality of care provided in State mental institutions; and (3) continued and expanded efforts to solve research and manpower problems in the mental health field.

A great deal has already been done to implement President Kennedy's proposals. First, Congress passed the Community Mental Health Centers Act, which authorizes the appropriation of a total of $150 million for grants to assist in the construction of community mental health centers in the 3 years beginning next July. Second, Congress continued support for a grants-in-aid program for comprehensive mental health planning, appropriating a total of more than $8 million in 1963 and 1964. Third, the hospital improvement projects program was launched, for which the Congress appropriated $6 million for demonstration projects to help State mental hospitals and institutions for the mentally retarded strengthen their therapeutic services and become an integral part of the developing community programs. And fourth, increased appropriations were made for the Institute's training and research programs, including an appropriation for $3.3 million for the inservice training of personnel in State mental hospitals and institutions for the mentally retarded.

Because of the great importance of the comprehensive community mental health centers, and because this is the first time the NIMH has submitted a budget to implement this newly authorized program, a separate statement has been prepared in support of this item under a wholly new appropriation—"The Construction of Community Mental Health Centers." Therefore, at this time, I shall report the progress we have made in the past year on all other new and contributing mental health activities.

PLANNING GRANTS

Closely integrated with and basic to the newly enacted community mental health centers legislation are the appropriations made by Congress in the fiscal years 1963 and 1964—over $8 million in all—for planning grants to facilitate the preparation of community and statewide plans for the new comprehensive community programs in which the community centers will be based.

The NIMH has made progress, over the last year, in implementing the planning grants program. Since announcement of the availability of the funds for planning appropriated in 1963, applications for planning of all the State mental health authorities have been approved by the Public Health Service, thus enabling the States to use these matching, grant-in-aid funds.

For the first time in the history of our country, each of the States will be able to formulate a comprehensive community approach to the problems of the mental illnesses as they affect its residents.

What is of even greater significance, however, is the fact that such a comprehensive planning effort is being made in mental health, which for so long lagged behind other health areas. The experiments we are undertaking in planning will, if we are successful, help our communities become capable of planning in other areas for changing social-medical needs.

As the planning grants program has developed in the past year, there is every indication that the new experiments in planning will be successful. First, the goals which shape these experiments have such a quality of human urgency that, in the variations to be found in planning activities across the country there has been a remarkable unanimity of purpose, and an intense quality of effort. Though reflecting the great variety among our States that characterizes our country, the State planning operations have in common a commitment to broad participation, to community orientation, to a setting of common goals, and to learning as a component of action.

The guidelines which were issued by NIMH assured that all proposals would have much in common in addition to the accepted goal of mental health planning. Funds were made available for such activities as the development and use of means for gathering data, the integration and analysis of information, the determination of needs, the selection of goals, priorities, and methods, and the allocation of available resources to achieve the selected goals. The State agencies, plus other public and private agencies and groups, were involved in planning, and the means and mechanisms for assuring their continued participation were required to be stated in their proposals.

We recognized the many differences between States and encouraged individuality of planning proposals. The existence of large metropolitan areas, thinly populated rural areas, meager service resources, special problems, and other individual State characteristics dictated the necessity for special provisions to meet these special needs.

Thirty-six States have already budgeted more than 75 percent of their share of the Federal planning funds available for salaries, travel, and consultants. An average of 6 new planning positions per State will be supported by these funds—a total of 337 new planning positions—and 25 States plan to create mental health districts or otherwise to divide their State geographically for planning purposes, and perhaps for operational purposes later.

In all but four States, planning staffs composed of many different types of personnel have been established, and these staffs are now involved in solving such very basic planning problems as how to relate the efforts of the public agencies with those of the private agencies, and how to inform communities of what is involved in the planning process.

Many of the States are setting up task forces to investigate problems of particular interest. Thus 29 States will have task forces investigating legislative and legal problems, 25 task forces have been established on the problems of financing, 24 on the recruitment and training of personnel, 23 on the problems of children and youth, and so forth.

In 16 States, the Governor himself has appointed the members of the planning body. In other States, the Governor has issued a proclamation with regard to mental health planning, reviewed and approved the planning proposals, or otherwise participated actively in this endeavor. In December, in the judgment of our regional offices, 75 percent of the States were making quite satisfactory progress in planning, as measured by the States own plans for planning.

In this discussion of the planning grants, partial though it is, one can see the flourishing of many creative efforts, nationwide in scope. A year from now, and 2 years from now, each State will be able to report what it has done, as well as what it intends to do.

Through the grant-in-aid program for planning, which Congress had the foresight to establish 2 years ago, we will be able to document our problems, mobilize our strengths, sharpen our thinking, give direction to our actions, and meet new problems. Furthermore, if, as we hope, the planning process becomes permanently imbedded in all States as it has in some, we shall have a mechanism which will help us to make continued progress in this field.

HOSPITAL IMPROVEMENT PROJECTS

To carry out President Kennedy's proposals concerning improved care in hospitals, the hospital improvement projects program, for which Congress appropriated $6 million, was initiated this past year. This grant program, accompanied by a continuing program of staff consultation and technical assistance, is designed to stimulate and assist State mental hospitals and State institutions for the mentally retarded in initiating a sequence of change and improvement which will spread throughout the entire program of the institutions. It is also designed to help them achieve a more positive role as an integral part of the comprehensive community programs in mental illness and mental retardation, and to help the communities benefit from the unique contributions the institutions can make to comprehensive community programs. I am again reminded of Dr. Adolf Meyer's commonsense psychiatry, and of his conviction that the State institutions would, in the future, bring "their unique experience within the reach of physicians and the public of their districts." "The larger State institutions," he pointed out, "follow the cases through all the stages * * *. They are in the position to show the communities not only the best modern work but also the failures of local civilization."

The experience of the State institutions and of their staffs in handling large numbers of critically sick and chronically sick people is a valuable mental health resource which must not be lost as we proceed to develop our comprehensive centers and programs.

The $6 million appropriated for the hospital improvements program for fiscal year 1964 will make possible at least one grant in each State which submits an approvable project. An individual hospital or institution may receive a maximum of $100,000 in any 1 year for a project or a series of projects, with projects of more than 3 years' duration being reviewed every 3 years. Projects will compete for the $6 million appropriated for this program, but they will not have to compete with all applications for mental health project grant funds, of which this appropriation is a part.

The response of the State institutions and of the State mental health authorities to the announcements of this grant program they received last October was most gratifying. By early December, the deadline for receipt of grant applications, 101 of the 289 eligible State mental hospitals and 65 of the 134 eligible State institutions for the mentally retarded submitted applications. In all, applications from 48 of the 54 States and territories were received. These applications will be critically reviewed for technical merit by a committee of outside consultants, and the committee's recommendations will be available to the National Advisory Mental Health Council when that body reviews the applications in February.

A review of these applications indicates that State agencies and institutions staff have accepted the spirit of the demonstration and stimulus aspects of the program.

A number of mental hospitals are proposing to use project funds to initiate as a demonstration the State's first specialized intensive inpatient treatment program for emotionally disturbed children and adolescents. Other institutions are proposing to start demonstrations of programs for other special need groups, such as the aged, who are often relegated to domiciliary and minimum nursing care. A number of the institutions are proposing demonstrations which, for the first time in the history of the institutions, will make it possible to show what a few trained staff, working full time and supervising and working with existing personnel, can do to improve the physical conditions and social and behavioral adjustment of seriously chronically ill patients.

In general, we feel that this new hospital improvement projects program will contribute much to the comprehensive mental health programs we are developing, and we are extremely grateful that appropriations for fiscal year 1964 have given us an opportunity to develop this program so promptly.

MANPOWER AND TRAINING

President Kennedy, fully realizing the problems of manpower and research in the mental health field, stated in his message:

"We must not relax our effort to push back the frontiers of knowledge in basic and applied research into the mental processes, in therapy, and in other phases of research with a bearing upon mental illness. I recommend an expansion of clinical, laboratory, and field research in mental illness and mental health * * *. Availability of trained manpower is a major factor in the determination of how fast we can expand our research and expand our new action program in the mental health field"

To implement this portion of the President's proposals, Congress, in 1964, appropriated $15,800,000 more in training funds than in 1963, and $10,170,000 more in research grant funds, including appropriations for the hospital improvement projects.

First, some brief words about our new inservice training program, for which Congress appropriated some $3.3 million for fiscal 1964. The long-range objectives of this program are: to increase the effectiveness of the staff in mental hospitals, in institutions for the mentally retarded, and in other community mental health agencies and services; and to translate rapidly increasing knowledge into more effective services to people.

Because personnel such as psychiatric aides, attendants, houseparents, and others similarly involved in direct patient care constitutes such a large and important resource in mental hospitals and institutions for the metally retarded, inservice training support was first extended to this general category of personnel. To date, almost 200 institutions have applied for these grants, and it is anticipated that approximately that number will be carefully and critically reviewd for possible support from fiscal year 1964 funds.

We expect the inservice training grants to become an increasingly important part of our total training programs in future years, for the success or failure of our new comprehensive programs will be largely determined by the quality—and quantity—of staff available to work in the programs.

To provide the comprehensive community mental health centers with an adequate number of properly trained people will require the rapid growth of all mental health training programs, and the rapid increase in the number of trained persons available to work in mental health programs. To meet this need, the NIMH estimates it will be necessary to double the present number of 45,000 mental health professionals within the next decade. This goal is by no means out of line with our needs when one recalls that the population of the United States is expected to increase by approximately 32 percent by 1980, and that a serious shortage of professional manpower already exists. Furthermore, we believe it is obtainable if we continue to develop our training programs at an accelerated rate.

Therefore, during fiscal 1964, thinking has been focused on how the Institute, given our current level of knowledge, could take significant steps toward the solution of the shortage. Obviously, many aspects of the manpower problems are not new. However, since our action programs are geared toward providing, in the future, a different working milieu—the Community Mental Health Center—for many thousands of workers, current approaches must be reviewed and, where necessary, revised. Only in this way will the services for which we are building the centers be available.

Highlights of progress in Institute training programs over the past year include:

> The addition of five new graduate and five new undergraduate programs in psychiatric nursing, bringing the total of graduate programs supported to 41, and of undergraduate programs to 104.
>
> The initiation of grants for 16 programs among the more conventional areas supported in psychology.
>
> The continued expansion in capacity and number of graduate psychiatry programs * * * the development of new programs in child psychiatry residency training, in community mental health, student health-mental health, and corrections * * * increased number of applications for support under the general practitioners program.
>
> The development in medical schools of teaching programs leading to the integration of the behavioral sciences into the education of the physician.
>
> The support for training in psychiatric social work in every accredited graduate school of social work.
>
> The steady increase of applications for the pilot projects program, which supports innovative training efforts with mental health relevance, from 12 in 1962 to 44 in 1964.
>
> The increased attention being given manpower needs in sociology and anthropology, in which only 240 Ph. D. degrees are granted annually, despite sharply increased demand.
>
> The awarding of 190 stipends in the biological sciences research training program.

The efforts the Institute is making to plan constructively for the future are epitomized by the current and projected activities of the manpower studies program. In the past year, this program has, for instance: (1) completed a survey of 2,300 mental health establishments which employ 44,800 professional personnel; (2) prepared two preliminary reports on a study of psychiatric aids covering such topics as educational background of aids, turnover, availability of training programs, salary, etc.

Finally, during the past year, the Institute has become fully aware that the shift in focus from the mental patient-hospital concept to the patient-community concept is moving training beyond the professional mental health worker to include many different types of persons who deal with mental health problems in the community. Training is being sought not only to provide the skills to deal with problems as they occur, but also to acquire knowledge to help prevent the problems and to minimize their disabling effects.

The prospect of the new era of continuous and comprehensive community care has had great impact on NIMH training programs, and this impact can be expected to make extraordinary demands on the Institute's training and manpower programs throughout—and beyond—the next decade.

RESEARCH PROGRAMS

The fact that we entering a new era of community care has also had its impact upon NIMH research programs. Mindful of the President's plea for "an expansion of clinical, laboratory, and field research in mental illness and mental health," the NIMH believes it has used wisely the $66,200,000 appropriated for this purpose by Congress in 1964. While continuing our program of basic research, we have strengthened our programs of clinical and field research, and of research that will help us plan for the new community programs and provide the knowledge needed if these programs are to be successful.

We are developing additional research endeavors into such problems as the planning process, the economics of mental illness and mental health, the effectiveness of certain types of treatment programs, the nature of various types of patient and population groups, and of the mental health problems within these groups. Such research is directed toward answering the question of, "How can you make effective care and treatment available in the community at a cost the community can afford to pay or is willing to pay?" It is concerned with the logistics of services.

Our interest in the economics of mental illness has led us to note carefully reports which indicate that the total treatment costs of patients from admission to a State hospital to discharge have, on an average, decreased in recent years. Though per diem costs have increased, the shortened hospital stays made possible by new treatment modalities have enabled one State to report a 40-percent decrease in treatment costs per person discharged from $5,027 to $3,109 over a 10-year period.

As encouraging as such a report is, we find it even more hopeful that a recent NIMH-supported workshop on day hospitals produced evidence that approximately half of all patients who apply for inpatient psychiatric treatment can be handled successfully on a day-hospital basis—and that a day-hospital program costs approximately 60 percent less than full-time hospitalization.

Since the number of older persons in our society is increasing rapidly, and since approximately one-third of the patients resident in public mental hospitals are older than 65, we have paid particular attention to the mental health problems of older persons in the past year. At the Langley Porter Clinic of the University of California in San Francisco, the Institute assisted research which compared the psychiatric problems of 600 persons over 62 years of age who were admitted to a screening unit of the clinic with problems of a sample of 600 persons over 62 living in the community. Among the clinic patients, a much higher proportion was found to be suffering from acute brain syndromes than was expected, thus indicating the need for more adequate facilities to deal with the physical illnesses that produce behavioral symptoms. Of the 600 older persons living in the community, one-seventh were found to be psychologically impaired.

In our intramural research facilities in Prince Georges County, Md. (the Mental Health Study Center), and in St. Elizabeths Hospital (Clinical Neuropharmacology Research Center) problems of community psychiatry are being intensively explored by field research methods. In the Study Center, these activities, based upon 15 years' experience in Prince Georges County, have been directed toward the systematic study of a wide range of community mental health and mental health related problems. Activities there have included a process analysis of community mental health planning at a local level, the effects of mental health services upon a class of nonachieving children, and a study of the backgrounds and mental health problems of juveniles reported as missing from home.

In the Study Center, the emphasis has been on the broad community. In the Clinical Neuropharmacology Research Center, the emphasis has been on the work of the clinical facility—in following a relatively large number of patients from the community into the Center's programs, during the period they are receiving treatment, and out into the community again. An extensive study of the life histories of a large number of mental patients have led investigators in the Research Center to develop longitudinal profiles of patients' clinical and psychosocial life patterns. These, the investigators believe, are particularly useful in supplying data from which to estimate the total treatment needs of a given population.

In our intramural laboratories located in the Clinical Center of the National Institutes of Health in Bethesda, our programs of basic research and clinical investigations continued to make contributions to a general theory of behavior. Many specific research projects have been designed to try to define the types and the timing of life experiences which form—and deform—personality. New methodologies have been designed to explore how the child develops within a family, how healthy adolescents master their life problems, and how a person's previous life experience affects the aging process.

The brief review just completed above, while hopefully giving some idea of the expanding parameters of our clinical, field and research laboratory efforts, do little to indicate the overall magnitude of our research programs, or their impact.

For this purpose, I would like to turn to a discussion of our research efforts in schizophrenia, which, from a public health point of view, is the gravest of all mental health problems—despite the fact that other mental disorders or problems may be as tragic in their impact upon some individuals and their families as schizophrenia.

The measure of the challenge of schizophrenia as a public health problem is revealed in our mental hospital and clinic statistics: in recent years, patients with schizophrenic reactions have comprised nearly 25 percent of all first admissions to public mental hospitals, and 50 percent of all resident patients. To solve this urgent public health problem, the Institute is supporting the work of researchers in the medical, biological, psychological, and social sciences, as well as the efforts of clinicians and community service personnel whose careers are devoted to the utilization of scientific findings.

From the inception of the NIMH research grant program in 1948 until the end of fiscal year 1963, 1,849 awards totaling $54,019,379 were made for projects in the area of schizophrenia; this represents 21 percent of the total number of grants and 27 percent of the total amount of funds awarded to date.

During the fiscal year 1963, nearly $14 million was devoted to research activities in the area of schizophrenia, including projects in the intramural program as well as awards made through the various Institute research grant programs. More than 370 projects relating to schizophrenia were supported through NIMH research grants during the year.

Represented here are projects of various types—from small pilot studies in relatively unexplored areas to the diversified activities of large clinical centers. The fields of study encompassed in research on schizophrenia range from the most molecular of the biological sciences to the broadest of the behavioral sciences. More than one-third of the NIMH studies in this area during fiscal year 1963 were in the field of clinical psychiatry; one-fourth were in various areas of psychology—primarily clinical, physiological, social, and educational; another fourth was comprised of studies in psychopharmacology, biochemistry, and physiology. The remainder spanned a variety of additional areas—including sociology, epidemiology, anthropology, public health, and administration. In the mental health project grant program, about one out of every three projects supported is concerned to some extent with the problems of the treatment and rehabilitation of schizophrenics.

Recent findings from this research effort have included the following:

* * * 60 percent of severely disturbed children are improved by presently available drugs.

* * * of former State mental hospital patients in New York City who were kept under continuous close supervision and given aftercare for 5 years, only 37 percent had to return to the hospital, and of the patients still in the community after 5 years, only 12 percent were unemployed.

While studies directly related to schizophrenia comprise a large portion of the NIMH research efforts, it must be emphasized that the eventual understanding of a complex disorder such as schizophrenia will depend not only on an exhaustive exploration of the schizophrenic process itself, but, more important, on an accumulation of knowledge regarding the fundamental mechanisms involved in the brain and in behavior. The causes of schizophrenia are still unknown, and the pathogenesis of the disorder undoubtedly involves complex interrelationships within the nervous system, as well as interactions among the nervous system, various other organ systems of the body, and the interpersonal relationships of individuals.

Basic information from a variety of sciences is, therefore, of prime importance. Basic research on normal thought processes, for example, is essential to an understanding of abnormal thinking; and fundamental knowledge of normal metabolism and of the biochemistry of the brain is essential to a comprehension of the ways in which these processes may be defective in a disorder like schizophrenia.

There are no assurances on the basis of current research that the schizophrenic illnesses which have challenged the best scientific minds for 2,000 years will be solved within the next year or two. There are, however, a gratifying number of new observations of considerable potential significance which demand further exploration; fortunately, an increasing number of competent investigators are interested in exploring them.

In general, I believe that the results achieved to date in our research programs and the progress of our current work warrants optimism about the future. In our basic research efforts, we are steadily accumulating knowledge on how the biological processes and psychological and social experiences determine the individual's level of adaptation. In our clinical and field research efforts, much is being learned which can be applied in the community mental health centers of the future.

CONCLUSION

With the addition on the national levels of the new programs outlined here and the already well-developed programs of research, training and grants-in-aid at the NIMH, plus the new community mental health center program, we should fulfill the promises of the new era of community psychiatry we are entering.

But, great as these promises are, they will be lost unless the momentum we have now developed is continued and accelerated. We must make the most of the promises and opportunities we now have or we shall lose them—and this effort must be made within the next two or three years.

The old system of care is deeply woven into the tapestry of our time. It lives in buildings, in the brains of men, in our statute books. It is reinforced each day we live by the subtle and not so subtle actions of hundreds and thousands of people. And somehow this tapestry must be rewoven, and rewoven by us.

If we are to see our efforts crowned with success, as must be the case, all that has been demanded of us in the past will be as nothing compared to the demands of the next few years. If we are to seize the opportunities opened up to us we must be prepared to dedicate ourselves to the work that must be done. If we do, the promises inherent in the new programs initiated by our late President and the Congress last year will become the realities, yes, even the commonplace, of tomorrow.

The request for 1965 is $188,917,000 as compared with an operating level in 1964 of $173,492,000. There is an increase of $15,425,000 which is spread among the activities of the Institute for ongoing and new programs. The increase is discussed in detail in the budget justification. The request for 1965 is distributed as follows:

Grants:	
Research	$76, 495, 000
Fellowships	8, 057, 000
Training	73, 213, 000
State control programs	6, 750, 000
Subtotal, grants	164, 515, 000
Direct operations:	
Research	11, 203, 000
Collaborate studies	3, 986, 000
Training activities	1, 088, 000
Professional and technical assistance	4, 224, 000
Review and approval of grants	3, 264, 000
Program direction	637, 000
Subtotal, direct operations	24, 402, 000
Total 1965 appropriation request	188, 917, 000

Dr. FELIX. With the committee's permission, I would like to address myself to some highlights in this statement and mention some accomplishments of the program, if I may.

PATIENT POPULATION DECREASE

It is with particular pleasure, Mr. Chairman, that I report that for the 8th consecutive year, without any exceptions, there has been a drop in the population of our State and county hospitals. As a matter of fact, I am particularly pleased because the drop this year is the second largest drop of any year since the decline began in 1956. The reduction this year was 10,753 patients, which was a decrease of 2.1 percent. The average decrease since 1955—that is, the average annual decrease, has been 1.2 percent.

This decrease is from a projected figure of which I have spoken before. What the figure would be this year had the trend continued as it had over a period of 9 years prior to 1956 is 661,000. The present figure is 156,000 less, or 23 percent below the projected figure.

Had this figure been the one obtaining today, it would have cost us in maintenance alone about $1 billion more than it has under the present situation.

Mr. FOGARTY. What do you mean by "maintenance" housing and care?

Dr. FELIX. Housing, care—everything but capital expenditures. I am not including capital expenditures. Cost of staff, housing, care, food, all of this. We take the per annum cost for the country as a whole for maintaining the patient in a public hospital for that year and estimate the number of patients we would have had that year and the differences between the estimated number and the actual number.

Now, I mention these figures for the last time, unless you want me to continue it in years to come, because these figures are getting so large and the improvement has gone so long that I would begin to question pretty soon how accurate these estimates would be.

I would then like to turn for a moment, if I could, to what the actual decrease has been. What I am going to give you now are not estimates; these are hard figures.

In 1955, which was the peak year, there were 558,922 patients in our public mental hospitals. By public, let me qualify by saying I mean State and county hospitals. This does not include Federal Government hospitals, VA, and so forth.

In 1963, at the end of the year, on the comparable day, there were 504,947 patients, or 53,975 less than the peak year. This is a drop of 9.7 percent. This is an actual drop. There are that many fewer patients in today than there were then.

These patients, these 54,000 patients, would have cost an additional $320 million had we had them in the hospitals.

Mr. FOGARTY. For 1 year?

Dr. FELIX. No, for the years since 1955.

Mr. FOGARTY. Since 1955.

Dr. FELIX. Some of these that have dropped out.

Let me give you a 1-year figure now that you have asked, Mr. Chairman. The difference between the number of patients at the beginning of 1963 and the end of 1963 is 10,753. It would have cost the taxpayer $11,800,000 to take care of those patients for 1 year in the hospital.

Now, this sounds good, and we should all, I suppose, feel some satisfaction about this, and I do, frankly. However, let me point out a few things that cause me some alarm. There has been either a decrease, or at least no increase in the numbers for every age group except two, and I ask you to listen to me because I think you will be as concerned as I.

INCREASE IN CERTAIN AGE GROUPS

In the group 15 to 24 years of age, there has been an annual increase of 5 percent in the number of patients in the hospital. That is 5 percent per year more each year. There has been an annual increase of 17 percent in the number of patients under 16 in our public mental hospitals.

Now, I will be the first to say the numbers involved are not great. I do not mean we have a sudden horrible situation on our hands. But any time we have a group, containing several thousand persons, which increases at the rate of 17 percent a year, I cannot feel comfortable about it, and I think I should communicate my discomfort to you.

Now, these two groups concern me so much because these are tomorrow's citizens. In fact, some of them are today's citizens. These are the two groups who particularly would benefit by care and treatment in their own communities if we had community facilities. I will address myself later to this when we discuss the community centers appropriation, but I would like to direct your attention to this now.

DAY-NIGHT HOSPITALS

Community resources for the treatment of emotional problems are beginning to appear over the country. But there is not much coordination between facilities.

I would like to show you some of the figures that indicate how much the situation has improved.

Before 1960 there were only 37 day care and night care hospitals in existence in the country. By day care and night care, I mean hospitals where a person can come in the morning, stay during the day, get whatever treatment is needed, go home at night. Or a person can go to work during the day, and many of them are able to do so, or take care of their families, as the case may be, and come to the hospital at night because they are unable to maintain a comfortable and productive existence at home during these night hours.

Thirty-seven of these hospitals were in existence before 1960. By the end of 1963, there were 120 of them in 32 States. The reports indicate that roughly one-half of the patients who formerly would have been admitted to 24-hour facilities can be successfully treated in day-night hospitals.

Further, these facilities cost less per patient. It is about 40 percent of the cost for 24-hour care. This is important also from the point of view of prepaid insurance plans. This begins to come down to a figure where we can talk seriously to some of these insurance concerns.

Also, these day and night care hospitals show a tendency to decrease depression and psychological regression. The patient's ties with his family and with his community are retained. I have spoken to you here over a number of years about the importance of maintaining ties to community and to family and what this means in terms of rehabilitation and in terms of actual improvement and recovery.

I said that there were 120 of these hospitals in 1963. We did a check during a week in May 1963 to find how many patients were being cared for. There were 3,600 patients in these hospitals that week.

Let me go now to another type of facility that is beginning to be developed very rapidly. In 1963, there were approximately 600 general hospitals in the country with psychiatric units and psychiatric services. It was only 2 or 3 years ago that I reported that there were 400. This is an increase of 200 in that length of time.

There were more than 211,000 patients admitted for treatment in these hospitals last year. The reason I put my figure this way is that we have tried to gather figures from all 600 hospitals, but this is a voluntary matter. Three hundred seventy-five of these cooperate with us. The 211,000 is based on data from 375 hospitals. So the true figure is some amount in excess of this.

About 75 percent of these patients return directly to the community. They do not have to go to any other type of institution.

OUTPATIENT CLINICS

In 1963 there was an excess of 800,000 patients treated in 1,776 outpatient clinics. I am rather interested in that figure for a lot of reasons. This is one of the ways we free ourselves from the current concept of the public mental hospital. This is the new revolution. Twenty percent of the patients seen in clinics were psychotic—I do not mean neurotic, I do not mean alcoholic, I do not mean nervous, anxious, or jumpy—20 percent were psychotic. This is in contrast to a figure of 11 percent in 1956. In the old days all of them would have gone to hospitals.

HOSPITAL COSTS

Now the population in our State hospitals is dropping. I have just told you that. The population of the country is rising as you are aware. I can tell you that the admission rates are rising. Now, this means only one thing; the average length of stay must be dropping if our hospital population is dropping.

This would mean, it seems to me, that the total cost per patient would be less, even though the per diem cost has gone up. It is with real satisfaction, for reasons I hope you will appreciate in a moment, that I make a report regarding this on the State of my residence, which is Maryland. If the experience of this State is indicative of anything, it is that we are going to be able to give much better treatment to many more patients at lower cost per patient.

Maryland reports a 40-percent decrease in treatment costs per patient discharged—that is not per day; that is from the day admitted to day of discharge—over a 10-year period. Forty percent less in 1963 than 1953.

In 1953 it cost $5,027 on the average to treat a patient from the time he was admitted to one of the State hospitals until he was discharged.

In 1963, it was $3,109. And I do not have here the exact figures, but the per diem has, I think, about doubled in this length of time. But the average length of stay has dropped.

Now, to me, this means a great deal, because these are my fellow citizens in my own State, in my own community, in my own neighborhood. And the reason that this has come about is because of maximum utilization of the fruits of research, applied by well-trained people. I am aware that this committee and the Congress are responsible for the fact that funds were made available for this to come about. And my satisfaction comes in that you have let me have the opportunity to work with you to see this happen. I am very, very grateful for this.

HYPOTHETICAL AVERAGE COMMUNITY

I have talked to you about patients returning to communities. I would like to take a moment, if I might, to have you look with me at a hypothetical community.

I wish you would assume with me for a moment that all the people in this country were mixed up together and divided up into groups of 100, and that they lived in blocks, residential blocks. You live in a block with 99 others, and I with 99 others, and so forth, so there were 100 in each block. What would these people be like?

Well, each block would contain 31 children and adolescents. It would also contain seven young unmarried adults, four men and three women. For the most part these would be either in the labor pool, Armed Forces, or continuing their education. There would be 23 married couples. There would be one widower. There would be at least four widows. In every other block there would be a divorced man. And in every block there would be a divorced or separated woman, likely to be under 45 and a mother of one or more children. The chances are one out of two that she would be working away from her house in order to support her children.

In one out of three blocks this year some youngster between the ages of 10 and 17 would appear before juvenile court on a delinquency charge. That is one out of every three blocks.

One out of every three individuals screened for military service will be found to be unfit for some reason, psychological or physical, and half of those found unfit would be for mental reasons. In every three blocks there will be at least one alcoholic. In every 40 blocks there will be one drug addict

In every block there will be at least 10 residents more than 65 years of age. Many of them will be living alone and experiencing increasing difficulty in getting along. And I would point out to you that this is the group with the highest suicide rate in the Nation.

If this is really an honest-to-goodness statistical block, one-fifth of the families will be living in poverty.

In one out of every five blocks this year some adult will be admitted to a mental hospital for the first time, and two persons in every five blocks will spend some time in a mental hospital. And 10 persons in each block this year will need—whether they get it or not is another story—some form of mental health assistance: clergy, family doctor, psychiatrist, psychologist, or something.

Now, this is what we are living with. These are the people that live around us and whom we serve. And I would like to address the rest of my remarks to how we are trying to serve them.

STATE PLANNING GRANTS

To meet many of the needs of the communities, as you are well aware, the Congress, through the action of this committee and its counterpart in the Senate, authorized for each of the past 2 years $4,200,000 for each year to be allocated to the States and matched by them for comprehensive statewide community-based, long- and short-range mental health planning.

I am pleased to report that all the States and territories with the exception of Guam submitted proposals and are now engaged in this plan.

In a high proportion of these States, these activities received the active support and participation of the Governors. The Governors have done such things as issued proclamations, appointed central planning committees, opened the first sessions of these committees, called statewide meetings, and otherwise demonstrated their concern.

By and large, these planning activities have taken the form of task forces working on special subjects. You might be interested in some of the most common ones: aging, alcoholism and drug abuse, mental health problems of children and youth, delinquency, financing of mental health programs, hospital facilities for the mentally ill at the community level, legislation and legal problems (including problems of the rights of the mentally ill), manpower, research and evaluation, training, and recruitment.

Now, a number of States are making special studies of large metropolitan areas, like Detroit, for example, Mr. Lesinski, where there are a variety of special problems.

Now, even this early in the game, 10 States have become so convinced of the worth of this activity that they have incorporated this planning into their regular program on State money as soon as our funds are finished. And three additional States say they will do so as soon as their legislatures meet.

The planning covers all phases of mental health problems in the States, including a plan for development of community mental health centers. As part of these programs in the States there have been launched, in the past year, two new programs which were authorized by the Congress. I would point out that the importance of these programs is clearly self-evident since, although I have given you the drop in the number of patients in our hospitals, I would point out that there are still over 500,000, over half a million of our neighbors who are still in public mental hospitals and that they are costing us and our fellow citizens who are not in there over $1.8 billion a year to maintain.

HOSPITAL IMPROVEMENT PROJECTS

Now, the first of these two programs which will assist in moving some of these patients out is the hospital improvement project program for which Congress appropriated $6 million for this fiscal year in which we are now operating. The program is designed to initiate a series of changes in each institution leading to improvement in care throughout the entire institution and to allow each institution to participate actively and constructively in statewide, comprehensive community plans.

No more than $100,000 can be awarded to any one project, and then only after the superintendent of the hospital has submitted plans and budget which has the endorsement of the State mental hospital authority, whoever that may be, for that State. All these projects are reviewed by a special study committee appointed as consultants to the Public Health Service and then again, as a second review, by the National Advisory Mental Health Council.

As of the last week in January, 105 State mental hospitals and 69 State hospitals for the mentally retarded have submitted applications. These hospitals represent 36 percent of the State mental hospitals and 51.5 percent of the State hospitals for the mentally retarded; that is, those that are eligible in the States. The applications were submitted from 48 of the 54 States and territories. About a third of the proposals are for projects designed to improve treatment and care of the chronic, longer stay patients, which is one of our great problems. About a fourth are designed to explore specialized services for children and adolescents.

I might say here one area that is more uncovered than any other in this whole field is the area of the adolescent. We do have—not enough, but we do have residential treatment centers for youngsters, say, 12 years of age and under. Then we have the adult institutions. But the forgotten person still in this whole network, and one toward whom I am dedicating my most serious efforts at the present time is the group from 12 or 13 up to about 18, the adolescent. I do not know if any of you remember a song that was popular 35 years ago (probably none of you do), but it was entitled "I Am Just an In-Between." This was the song of the adolescent. And here again they are just "in-between." They are too little or they are too big.

More than one-fourth of these applications bear specifically on strengthening continuity of service from the hospital into the community. That is a transitional kind of service.

I have been profoundly impressed with the essential soundness of most of the basic ideas proposed and of their possibility for eventual implementation in many States, not just the ones applying.

INSERVICE TRAINING

The second program is one designed to assist the States and institutions in improving and developing inservice training for their personnel. In fiscal year 1964, Congress appropriated $3,300,000 for this purpose. A long-range objective is to increase on a continuing basis the effectiveness of available staff in the hospitals for the mentally ill and mentally retarded. Hospitals, as in the case of the hospital improvement projects, apply through the superintendent, or the superintendent applies and it must go through the State hospital authority and have his endorsement and backing. The applications are reviewed by a special committee of consultants to the Public Health Service and by the National Advisory Mental Health Council.

I might say in both of these programs there will be a special meeting of the Mental Health Council, a 2-day meeting, in April at which these applications for participation in both of these programs will be considered.

Applications have been received for this program from 49 States and territories. To date 146 hospitals for the mentally ill and 82 institutions for the mentally retarded have applied for grants. This constitutes 51 percent of the hospitals for the mentally ill and 63 percent of the institutions for the mentally retarded, that are eligible.

We laid a lot of groundwork for this before we launched the program. In 1963, we held a series of 7 regional conferences at which over 700 State leaders participated. These included some of the Governors of the States, as well as legislators, heads of State institutions for the mentally ill and mentally retarded, members of their staffs, university presidents, university deans, department heads in universities, members of their faculties, and so forth.

To the best of my knowledge, this is the first time that representatives from mental health service agencies and institutions of higher education have sat down together and discussed over a period of time in a very serious way inservice training of subprofessional personnel in our hospitals.

There have been several hospital projects supported by the Institute of Mental Health over the past several years, the results of which have given us considerable optimism. If I may have a moment, I would like to mention just a few of these to show you some of the things that are hapepning and why I feel with all the sincerity I can put into it—that if we can launch this program in the communities, if we can continue the way we are going now, if we can continue to have your support and encouragement as we have had in the past, we are going to move many of these people out of these hospitals.

I said a year or two ago, and I say again, I believe that we can change the character of these hospitals. And we can reduce them in size by 50 percent in the next 10 or more years, 10 or 15 years, if we just keep plugging at it. I think we have shown that already by what has happened.

HIGHLIGHTS OF SPECIFIC HOSPITAL PROGRAMS

Let me tell you about some of these things. At the Massachusetts Mental Health Center in Boston, they have a community psychiatric extension service for patients placed on the waiting list of the mental health center. These patients are taken care of at home. One-half of the patients seen here did not require hospitalization. They are helped by psychotherapy, drugs, social case work, vocational counseling, et cetera.

A very, very interesting program has been developed through a grant from us at the Evansville State Hospital in Indiana. That is a homemaker service. It is being integrated into the social service department of the hospital to minimize the patient's and family's fears and assist in keping the home together until the patient comes home. These homemakers are wives and mothers. They are used during the period of hospitalization, and for a time when the patient returns to the family, if still needed. This program makes it possible to plan for much earlier return home for many of the patients.

In each of the cases selected for service it is possible for the family to continue as a unit in the community until the hospitalized patient's return. That means they did not have to send the youngster off to grandma's or to the neighbor's; they could stay at home and live as a family until the mother came home. The length of service provided varies depending upon the needs, a minimum of 2 weeks, maximum of 25 weeks.

At the State hospital in north Idaho, they have a family care program in which they are taking mentally ill and mentally retarded from the hospital and placing them in homes in the community. About 80 percent of the patients so placed did not have to return to the hospital again. They found something interesting here we should have known if we had thought about it, and that is if you place two or more patients in the same home, they get along better than if they are alone. They progress more rapidly.

At the Langley Porter Psychiatric Institute in San Francisco, they began to examine patients over 60 years of age admitted to the San Francisco General Hospital for treatment of acute mental illness. They found that a high proportion of these suffered from organic conditions, such as cardiac failure; malnutrition; cerebral vascular accidents—that is; strokes; and alcoholism. Once they were able to bring the patients' physical condition under control or relieve it, a large proportion recovered psychiatrically and were able to go home.

I think this has shown something that will be important in all of our community programs, and that is that when people over 60 years of age begin to develop physical difficulties, they should be carefully and continuously followed. That does not mean you have to sit on their doorstep all the time, but such supervision will prevent and forestall serious mental symptoms which can develop.

In a program in New York City, they have been treating children in an outpatient situation who were so emotionally disturbed that they could not go to school. By treating them with drugs, they have been able to get one-fourth of them back to school, another half of them into group activities and special school classes. So they are not going without education.

I have reported in the past about the Manhattan Aftercare Clinic in New York. We now have a 5-year followup on that project. Only 37 percent of the patients treated by drugs and therapy, including home visits, during 5 years, have had to go back to the hospital, and only 19 percent of them in the first year. This contrasts with 37 percent of the control group which had to go in the first year and a total of 50 percent before the 5-year period was up.

Now, these patients have been carried on a maintenance dose of a tranquilizer, in most cases it was chlorpromazine, during the 5 years. There have been no major side effects observed; they have been closely followed. This is necessary, of course. When the patients stopped the drug, there was often a recurrence of the symptoms; and of the patients still in the community after 5 years—and this is 63 percent of the original group—88 percent are either self-supporting or partially self-supporting or are working as housewives and homemakers, and satisfactorily so.

Mr. FOGARTY. Who started this program?

Dr. FELIX. Elsa Kris, was it not? Dr. Elsa Kris, K-r-i-s.

The Manhattan Aftercare Clinic is a followup service of the New York State mental hospital system and she is director of a research treatment program within the Manhattan Aftercare Clinic.

Mr. Fogarty. Did it not have anything to do with the Rockland State Hospital?

Dr. Felix. No, sir, it did not.

Mr. Fogarty. All right.

Dr. Felix. A similar followup study has been done in Louisville with comparable results. I am not going to bother you with those findings now because I want to address myself to one or two other points, and I have taken all too long.

PSYCHOPHARMACOLOGY

I would like to address myself for a moment to some of the new findings in the psychoactive drugs. As you know, our psychopharmacology service center has been running a series of studies through a group of cooperating hospitals, and I would like to report on a few of these studies.

In the collaborative study in which nine hospitals were involved, they have been testing three drugs that belong to the phentothiazine groups. These drugs are chlorpromazine, fluphenazine, and thioridazine. I do not have the trade names. I deliberately try not to remember trade names because I am looking at the chemical substances.

You remember, gentlemen, in years past I said our objective was to try to find a drug specifically effective for a specific condition, so that we can say for this condition, everything else being equal, that we will give this drug rather than some others, thus being able to mount an intelligent attack upon this problem. We have found that these three drugs are not just merely tranquilizers, but they actually have a specific antischizophrenic effect. I do not know why. This is an empirical finding. We will worry about the why as we can get to it. We have found out something here that is worth capitalizing on.

These drugs apparently have their effects on symptoms generally considered to be characteristic of major schizophrenic illness and generally considered not to be responsive to tranquilizer treatment. Some of these symptoms are slowed speech and slowed movement, indifference to one's environment, poor self-care, and inadequate emotional response.

Now, in addition to relieving these symptoms, the drugs also tend to prevent the occurrence of these symptoms in patients who are diagnosed as schizophrenic and admitted to the hospital without the symptoms. In a significantly higher proportion of cases, it is found that these symptoms do not occur in patients who are on these drugs than in patients who are not on these drugs.

Last year I mentioned another phenothiazine, acetophenazine and said it seemed more specific for paranoid schizophrenics. This is being checked out further in a double-blind study using some other drugs as well to see whether this still holds up.

Other studies indicate that one of the energizing group, imipramine, used for the treatment of depressions, has in addition a dramatic and specific effect in relieving chronic anxiety symptoms in patients who failed to respond to tranquilizers, or even in some cases to electroshock therapy. This is of particular interest because these patients were not depressed and this drug was originally thought to be of primary use in depression.

One final thing, and I will not bore you with further information of this kind. Another psychoactive drug, triperadol, not a phenothiazine at all, seems to possess a special usefulness in the treatment of underactive, retarded, chronic schizophrenic patients.

Gentlemen, these are some of the developments of the past year. There are others I could give you. Time rushes on. I would only say that these are some of the reasons why I feel justified in coming before you to request $188,917,000 for the operation of this program during fiscal 1965.

SUMMARY OF BUDGET

Mr. FOGARTY. Thank you, Doctor. That is a very good statement.

Taking all the adjustments for comparability into consideration, the funds for 1964 total $173,492,000.

Dr. FELIX. Yes, sir.

Mr. FOGARTY. And the request for 1965 is $188,917,000, an increase of $15,425,000.

Dr. FELIX. Yes, sir.

UNOBLIGATED BALANCE

Mr. FOGARTY. Of all the Institutes, I am most surprised at you having an unobligated balance. The justifications indicate that you will have an unobligated balance of $2,673,000 at the end of the year. What happened?

Dr. FELIX. Mr. Chairman, that is an unobligated balance because it is an unprogramed reserve. These funds, which constitute less than 1.5 percent of the appropriation for last year, were not programed. For one reason, we were not exactly sure how we wished to utilize the money at that time, and second, I felt it wise not to tie up every cent of our money with programs so early in the year. The money, I understand, would be available if properly justified any time during this fiscal year.

Mr. FOGARTY. Are you going to use that $2.6 million?

Dr. FELIX. We may very well call for some of it.

HOSPITAL IMPROVEMENT GRANTS

Mr. FOGARTY. The largest increase is $10,485,000 for research grants. Over half of this is to double the hospital improvement program from $6 to $12 million. I thought these grants were to improve the service with knowledge you already have, rather than for research. Am I wrong in that assumption?

Dr. FELIX. The $6 million you are talking about?

Mr. FOGARTY. $6 to $12 million.

Dr. FELIX. It will improve service, it will demonstrate new ways of utilizing available information. It will make it possible in a very small unit of the hospital for the staff to try out and adapt to their peculiar situation various kinds of techniques.

These funds are not being used for regular research projects. They were defended last year, and I defend them this year again specifically for this purpose, for the hospital improvement projects program.

Mr. FOGARTY. In addition to these grants, you also make regular research project grants to the same hospitals?

Dr. FELIX. It would be possible if they have a research program. In point of fact, very few of our regular research project grants go to our public mental hospitals.

However, if such a hospital is studying the effects of a phenothiazine drug on schizophrenia or the response of some animal to electrical stimulation of a nerve or something like that they are eligible for regular research grants if their project meets the criteria and is recommended for approval by the scientific review committees and the Council.

GUIDELINES FOR PROGRAM

Mr. FOGARTY. What guidelines do you have for this new program?

Dr. FELIX. You mean the hospital improvement program?

Mr. FOGARTY. Yes.

Dr. FELIX. In no case will a request be granted for more than $100,000 in any year. The program in any hospital will not run more than 10 years. The hospital may, however, during that time, run a demonstration for 3 or 4 years and then, on reapplication and approval, begin another demonstration important to the program of the hospital. The application must be made through the superintendent of the hospital and have his active support. We consider this vital. If the superintendent is not interested in improving his hospital, whatever we do is not worth much. We have found no cases yet where this is not true, I might say. We must also have the endorsement of the State authority responsible for public mental hospitals in the State, and not only his endorsement, but he must set forth how this project is a part of and fits into his total State plan which is being developed with the assistance of the Federal planning grant money.

The demonstrations in these institutions must be available for visitors from other hospitals to see, so that they can learn thereby and profit therefrom.

I might ask our Deputy Director, Dr. Yolles, if I left something out?

Dr. YOLLES. No; I think you have covered it.

Mr. FOGARTY. What is the minimum grant?

Dr. FELIX. Any amount.

Mr. FOGARTY. Anything up to $100,000?

Dr. FELIX. Anything up to $100,000. If they want $500, we will be happy to cooperate if it is a good project.

Mr. FOGARTY. When this was being considered last year, there was some objection to this program, as you know. One of the objections was why should we just hand out to every State hospital $100,000.

Dr. FELIX. Yes, sir. I attempted to explain that. My contention was that we were not "just handing out $100,000 to every State hospital." I pointed out that, in the first place, $100,000 in the total budget of one of these hospitals is such a miniscule amount of money, it would not be worth expending much effort for this purpose alone. I pointed out there would be a very critical, hard-boiled, double review of all of these projects.

I think one thing that may have created some misunderstanding or apprehension was something that I said then. I wanted it understood clearly, and I repeat it now, my intention—unless the committee wishes to countermand it—is that eventually I hope to see this program spread to involve every hospital for the mentally ill, every hospital for the mentally retarded in this country, because I think every hospital, without exception, needs the stimulation and inspiration of such projects in order to improve the care of their patients and to get more patients out of the hospital faster.

I pointed out that it had been our experience that these hospitals were hungry for the opportunity to demonstrate some of the things which they cannot do on their own because in too many cases—in a great number of cases—the budgets of these hospitals are so completely line items that they do not have even a few thousand dollars free to move into an area like this.

Mr. Fogarty. Very few State hospitals carry on research programs as such, do they?

Dr. Felix. That is correct.

Mr. Fogarty. I was thinking about my own State in particular.

Dr. Felix . That is correct. Although, as you are aware, you and I were there when the new geriatric building was dedicated several years ago, it was our hope then, and there have been some efforts in this direction, that there would be research, particularly in the area of the elderly patient.

Mr. Fogarty. They are doing research now; but prior to that, no one seemed to take any interest in it.

How many grants have already been made?

Dr. Felix. In this hospital improvement program?

Mr. Fogarty. Yes.

Dr. Felix. None, sir. As I said, the council meets in April when we will review the applications. We have had one meeting of the committee to look over about half of the applications. The committee meets again to look over the other half.

Mr. Fogarty. Money was only made available a short time ago?

Dr. Felix. Yes, sir.

Mr. Fogarty. $6 million.

Dr. Felix. The money was only made available a short time ago. As you remember, the appropriation came quite late in the year and we wished to give the hospitals all the time we possibly could under the fiscal regulations to plan and think this through.

Mr. Fogarty. Is there any requirement that the State increase its support for the institution receiving one of these grants?

Dr. Felix. No, sir. It is encouraged. As we consult with the States, we point out what can be done if they are able to increase the amount by some of their own funds. Since this program comes under the category of research projects—this is a subgroup under the heading "Research projects" which we have defended here all these years, it is not money which is matched. I would be most uncomfortable if we were to introduce into this research grant program a matching contingency or matching requirement, because if you do it in one area, you can do it in another, and I do not know where this would end.

PLAN TO PHASEOUT PROGRAM

Mr. FOGARTY. Do you intend to taper off this special support or continue it indefinitely?

Dr. FELIX. Hospital improvement grants?

Mr. FOGARTY. Yes.

Dr. FELIX. It will be tapered off. As rapidly as the Congress will permit me to do so, I would like to increase coverage to all of the hospitals, as I said. But in no case will the hospital be assisted under this program for more than 10 years. Those hospitals that would get their grant this year—it would be able to come late in the year, so let us say 1965—no hospital receiving the grant now would be able to receive a grant out of money appropriated later than that for the year 1975. The average length of time must, of course, depend in part upon the rate of development of our projected community mental health centers.

Am I correct?

Dr. YOLIES. Yes.

FUNDS FOR NEW RESEARCH PROJECTS

Mr. FOGARTY. For your regular project grants, you have an increase of $3,883,000, which you estimate will support 87 more projects in 1965 than in 1964. However, the increase in the new projects is only six, or less than 1 percent. This looks to me as if you are losing some momentum, are you not? Your increase in new projects is only six.

Dr. FELIX. Yes. The budget folks briefed me on this. It is not like it looks. But may I ask Mr. Van Staden to explain it?

Mr. FOGARTY. Certainly.

Dr. FELIX. I will just get myself in trouble, because I do not fully understand it.

Mr. VAN STADEN. It is really more than a technical budget explanation. All the institutes, and we among them, submitted our total research grant estimate, and in our case there were several kinds of major programs that fall under the budget category of the research grants program, one of which was the one just described. Another one was our psychopharmacology program, another was our mental health project grants program. So in establishing priorities on the basis of the overall NIH requirement, the special programs had to be considered before getting down to the regular conventional research project grant requirement within the amount that was allocated to this Institute. Furthermore, when you take into account the amount that has to go to continuation to carry the ongoing programs, by subtracting this is what was left for new projects—in our case six more new ones than last year.

Dr. FELIX. Am I correct, Mr. Van Staden, that actually the new grants will be 705?

Mr. VAN STADEN. 705.

Dr. FELIX. So that will be six more new than last year.

Mr. FOGARTY. That is what I said.

Dr. FELIX. We will have 705 new grants.

Mr. FOGARTY. That is what I said. The increase in new projects is only six.

Dr. FELIX. That is correct.

Mr. FOGARTY. I do not imagine you have gotten what you asked for, have you?

Dr. FELIX. Well, no, sir. One never does.

Mr. FOGARTY. I cannot blame you. I am not blaming you for it.

I assume you will get many more approvable new project applications in 1965 than you will be able to fund, will you not?

Dr. FELIX. Could well be.

Mr. FOGARTY. Is there any question about it in your mind?

Dr. FELIX. You understand, sir—I know you do, but I wish to be sure that I make myself clear—I am enthusiastically and with real serious intent defending this budget as a good, sound budget.

Mr. FOGARTY. I know you are.

I thought there was a memorandum distributed, just after we started hearings, that we wanted just as much attention paid to the fact that when you are asked a question by a member of the committee, that you give your best professional judgment, regardless of any other orders that might have been given to you, verbally or in writing; as is paid to the fact that you are to support the budget unless directly asked for your personal opinion.

Dr. FELIX. I am aware of that.

Mr. FOGARTY. That takes you completely out from under restrictions of the budget.

Dr. FELIX. Well, sir, I am kind of a conservative person, as you know.

Mr. FOGARTY. I know. You have always been too conservative, I think.

Dr. FELIX. Of course, we could use more. If there were no other consideration in the Department of HEW but NIMH, we could use considerably more.

Mr. FOGARTY. Forget about all the rest of the problems; talk about your own shop.

Dr. FELIX. Yes, sir; we could use more.

SCHIZOPHRENIA

Mr. FOGARTY. Now you are making some progress in research on schizophrenia. What percentage of the mentally ill are schizophrenics?

Dr. FELIX. About half of the patients in our mental hospitals are schizophrenics at the present time.

Mr. FOGARTY. That has been the percentage for some years.

Dr. FELIX. Yes, sir.

Mr. FOGARTY. Does the percentage of all hospital beds occupied by the mentally ill remain about the same, 50 percent?

Dr. FELIX. About half of all hospital beds are filled with the mentally ill, but about half of the mental hospital beds are filled with schizophrenics, old or new. Some of them have been there for some time.

Mr. FOGARTY. Do you want to talk about research progress in this area of schizophrenia? I had someone write to me from California that they thought they ought to start an institute on schizophrenia.

Dr. FELIX..There has been a briefing statement supplied me by my staff for purposes of these hearings which, if the committee wishes, I could supply for the record, which amplifies, goes into considerable detail.

Mr. Fogarty. All right, we will put that in the record.

Special Report—Schizophrenia

INTRODUCTION

The challenge of schizophrenia continues to demand the intensive efforts of hundreds of scientists. clinicians, and community service personnel whose work is supported by the National Institute of Mental Health.

The measure of the challenge is well defined by national data collected by the Institute's Biometrics Branch. In 1961, nearly one-quarter of all first admissions to public mental hospitals were patients with schizophrenic reactions; and, half of the patients resident in the public mental hospitals in 1961 were also schizophrenics.

To solve the urgent public health problems posed by schizophrenia, the Institute is supporting the work of researchers in the medical, biological, psychological, and social sciences, as well as the efforts of those outside the laboratory whose careers are devoted to the practical utilization and field application of scientific findings.

This report provides a summary of the Institute's research activities concerned with schizophrenia, as well as those activities directed toward the maximum utilization in institutional and community settings of new research developments. A description is also furnished of efforts by NIMH to provide increased resources of trained personnel for both research and clinical work.

RESEARCH PROGRAMS

Scope

From the inception of the NIMH research grant program in 1948 until the end of fiscal year 1963, a total of 1,849 awards totaling $54,019,379 were made for projects in the area of schizophrenia.

This represents 21 percent of the total number of grants and 27 percent of the total amount awarded to date.

During fiscal year 1963, nearly $14 million was devoted to intramural and extramural research in schizophrenia. More than 370 projects relating to schizophrenia—from small pilot studies in relatively unexplored areas to the diversified activities of large clinical centers—were supported during the year through NIMH research grants totaling nearly $13,200,000.

Schizophrenia research ranges from the most molecular of the biological sciences to the broadest and the behavioral sciences. More than one-third of the NIMH studies in this area during fiscal year 1963 were in clinical psychiatry; one-fourth were in psychology—primarily clinical, physiological, social, and educational—nearly 12 percent in psychopharmacology, 10 percent in biochemistry and physiology, and another 8 percent in sociology, social work, epidemiology, and anthropology. The remainder included such areas as public health, nursing, history, and administration.

A summary of the Institute's research effort in schizophrenia follows. Intramural studies are included, but unless otherwise noted. references are to projects supported through NIMH grants. Specific projects are cited as examples of a larger number of related projects in a particular area. While the grouping of projects under specific headings is sometimes arbitrary, it indicates the general scope of research in schizophrenia.

Biological factors

Understanding a clinical disorder such as schizophrenia requires a vast armamentarium of basic information about the workings of the nervous system and of behavior. This section deals only with research specifically concerned with biological approaches to schizophrenia.

Although most of the current interest in schizophrenia is along biochemical lines. recent developments in instrumentation have made possible a renewed quantitative exploration with electronic averaging devices, of electrical activity of the brain. of the processes involved in the registration of sensory information at the cortex, and, to some extent, its translation into motor activity. The remarkable feature of these studies is that they can now be performed through the intact scalp and yield information much more definite, reliable, and quantifiable than the classical electroencephalogram. One such study indicates that the new techniques are capable of demonstrating a significant difference in certain of the measured parameters between psychotic patients and normal control.

More definitive characterization of the neurophysiological alterations and their relationship to specific psychiatric syndromes, including schizophrenia, are currently underway.

In the biochemical sphere, research has centered upon two areas: The possibility that an abnormal protein in the blood of schizophrenic patients is responsible for the disorder, and the possibility that some forms of schizophrenia may be associated with an abnormality in biological transmethylation.

Interest in a protein constituent of the blood in schizophrenia was stimulated by a report from Tulane in 1957, that a protein fraction in the blood in schizophrenia was capable of causing some of the symptoms of that disorder when injected into nonschizophrenic volunteers. The substance, given the name "taraxein," apppeared to have some relationship to ceruloplasmin, a copper-containing globulin found in normal plasma. Attempts to replicate the production of psychotic symptoms in volunteers by injections of material similarly prepared were not successful, and to date the original findings have not been confirmed in a significant and well-controlled series. Following this report a number of groups have independently obtained evidence supporting thesis that an abnormal protein is present to a greater extent in the blood of some schizophrenics than in normals and that this substance is capable of producing certain behavioral, metabolic, or cellular changes in lower animals. However, these studies have not to date been successful in producing a purified, reasonably stable material or in characterizing it beyond its presence in the alpha-globulin fraction.

One group of investigators, by an ingenious and careful series of studies, has found evidence for an antigenic abnormality in the pooled serum of chronically ill schizophrenic patients. This was done by sensitizing animals with serum from schizophrenics, desensitizing with serum from nonpatients, and challenging with the sensitizing pool. A sufficient number of appropriate controls has been performed to suggest that the abnormal antigen is not simply a consequence of psychiatric hospitalization and that it may be of more than incidental significance in schizophrenia.

Another investigator has found evidence for the effect of plasma from schizophrenic patients upon learning and retention of learning in the rat. Other investigators have found a slowing of certain types of motor activity in rats injected with fractions of the serum of psychotic patients of a greater degree than that found with normal plasma fractions. Scientists at one clinic have reported alterations in the ratio of lactate to pyruvate produced by chicken erythrocytes incubated in plasma, and certain plasma fractions of some schizophrenic patients as compared to normal controls. Another investigator has reported a higher incidence of hemagglutination reactions in the serum of patients in State psychiatric hospitals as compared with blood donors, and although this phenomenon has a high incidence in schizophrenia, it is also present significantly in other psychiatric disorders.

Before his appointment to the National Institute of Mental Health, one senior investigator made an important contribution to basic biochemistry in elucidating biological transmethylation (the mechanism whereby the methyl group is added to a large number of important substances within the cells of plants and animals), crucial in a wide variety of normal biochemical processes responsible for the synthesis of a number of agents, of which adrenaline is an outstanding example, and for the normal metabolism of a number of other substances. After his appointment to this Institute it occurred to him, and independently and simultaneously to a group in Canada, that a number of foreign substances, of which the best example was mescaline, which were psychosis inducing were also methylated compounds. The hypothesis was put forth that in schizophrenia such compounds might be produced endogenously from normal metabolites in excess amounts.

In the past year, one grantee has demonstrated the presence in the urine of a high percentage of schizophrenic patients of a substance (3,4-dimethoxyphenylethylamine) which is a dimethylated derivative of dopamine, a normal body metabolite, and closely related to mescaline, which represents a trimethylated dopamine. This scientist has also reported the ability of liver cells to produce this substance from dopamine.

These findings are clearly compatible with, but do not fully confirm, the hypothesis that the process of biological transmethylation is somehow disturbed in schizophrenia with the production of excessive amounts of methylated derivatives of normal metabolites capable of inducing some of the symptoms of schizophrenia. Although methionine is the only one of a large number of amino acids capable of potentiating schizophrenic psychosis, it has not been established that the clinical changes resulted from any methylated derivatives, and the possibility that this was a nonspecific toxic psychosis has not been ruled out.

Although the original investigator who reported the dimethyldopamine in the urine of schizophrenic patients was unable to find it in normal urine, other workers have found it in normal population; albeit not as frequently as in schizophrenia. There is only preliminary evidence that this substance is produced endogenously in the body rather than being a dietary component, and no direct evidence that it is responsible for any of the symptoms of schizophrenia. Here again, as in the case of the serum protein factor, there are some interesting findings compatible with a provocative hypothesis, but the findings and the hypothesis are still in the earlier stages of confirmation and evaluation.

Psychological, social, and cultural factors

Investigators continue to regard as crucial the role of psychological, social, and cultural factors in the etiology and course of schizophrenia.

A number of projects are studying the impact of the family on schizophrenic illness. Noting that schizophrenic patients tend to come from seriously disturbed homes, one research team has intensively studied 16 families having a schizophrenic child and at least 1 other child, seeking why 1 child had become schizophrenic and not the others.

The findings, however, do not show the siblings of schizophrenics to be entirely free from mental illness. Among the 24 siblings of the patients, as many were found to be psychotic as reasonably well integrated, and all except 5 or 6 suffered from serious personality disorders. A definite sex linkage is reported: only one sibling of the same sex as the patient was considered reasonably stable, and no sibling of the opposite sex from the patient was found overtly psychotic. The researchers report that the demands of development confronting children of opposite sexes in a given family were very different, and that even those close in age had been subjected to quite different intrafamilial influences.

Another study has focused on relation of birth order to schizophrenia. More patients (both recovered and unrecovered patients in State hospitals) were found among the younger rather than the older siblings in large families (five or more children); there were more females than males. The investigators suggest that a large number of older siblings increases the likelihood of schizophrenia. They report, too, that patients with a large number of older siblings seem less likely to recover than those with few.

It seems consistent with available information about schizophrenia to look for the responsible causes in the patient's family environment. A large number of older and therefore more capable siblings in the family may cause considerable stress—especially in combination with the inadequacies reported as characteristic of parents of schizophrenic patients.

An intramural study has revealed a significant difference in birth weight of identical twins, when one is schizophrenic. The schizophrenic twin was generally smaller and weighed less at birth. The investigators hypothesize that the physically weaker twin is drawn into a more intense and pathological relationship with the mother.

The role of the broader social and cultural environment in schizophrenia is the subject of a number of investigations. Such studies seek to differentiate cross-cultural aspects of behavior disorders from those determined by forces unique to a given culture. Emotional disorders are generally regarded as stemming from a combination of biological, psychological, social, and cultural factors. The impact of cultural factors on behavior can best be understood, then, by studies of attitudes and behavior conducted within a specific, circumscribed cultural setting.

In one such research project, for example, field studies have been carried out among Navaho, Zuni, Taos and Western Apache Indians in an attempt to describe all cases of mental illness that have occurred in these groups. Conceptions of mental illness and psychotherapeutic procedures are being investigated in order to help define the specific patterns of psychopathology related to cultural factors.

In another project, the investigator is attempting to further our understanding of the important relationship between goal-striving behavior and mental illness by studying a specific group—an American Negro community. The investigator hypothesizes that stress resulting from failure or anticipated failure to reach important goals (occupational, economic, etc.) will be significantly related to mental illness. Data are being gathered from 1,500 randomly selected individuals living in Philadelphia. This study is typical of those intended to add to our store of knowledge about an important scientific issue: What is the impact of the social and cultural environment on mental illness?

The intramural study of the relationship between psychological and cultural factors is being pursued thorugh intensive investigations of family dynamics in schizophrenia—both in the United tSates and in Beirut, Lebanon. The question posed here is whether the behavior patterns found among families of schizophrenics are specific to a particular culture. The Beirut project is supported in part through the intramural program and in part through an institute research grant. Armenian, Moslem, Arab, and Christian Arab, and Druse families are being studied intensively with techniques similar to those in the intramural program.

Epidemiological factors

Many etiological factors—genetic as well as social—can be substantially clarified through carefully controlled epidemiological studies which focus on the relationship between biological and environmental variables on the one hand, and the incidence of mental disease on the other.

One such project involves an investigation of trends in mating and fertility among schizophrenics during the past few decades—focusing especially on changes resulting from application of modern treatment and rehabilitation, including drugs. The sample being studied includes couples in which both man and wife have been hospitalized for schizophrenia in New York State hospitals.

Preliminary results indicate a substantial increase in the fertility rates of schizophrenics hospitalized during the period 1954–56, as compared with those admitted in the period 1934–36. The increase is relatively larger than that for the general U.S. population during the same time. The investigator is planning to identify the consequences of these changes in terms of future prevalence rates, and is collecting detailed data on the health status of children born of schizophrenics. The sample of children born of two schizophrenic parents provides a particularly significant source for the study of preclinical indicators of schizophrenia at the biochemical and chromosomal level.

Population transiency is generally regarded as indicative of unstable community organizations and the formation of relatively few satisfying interpersonal bonds. The aim of another study, therefore, is to test the hypothesis that high rates of population turnover are associated with higher rates of hospitalization for schizophrenic disorders.

Do discharged psychiatric patients endanger society? With the widespread use of new chemotherapeutic methods of treatment, more patients are being returned to the community whose symptoms may still be active. One might expect an increase in dangerous behavior if these people are truly dangerous as a result of their illness. One research endeavor—based on surveys of arrest rates—seeks to determine if this is true, and to help develop improved criteria for hospital discharge.

Epidemiological studies in cross-cultural settings are important in uncovering ways in which cultural factors influence not only the incidence and manifestations of psychopathology, but the modes of treatment as well. Many countries, for example, report a low incidence of hospitalized mental patients, and in one project an attempt is being made to determine if the incidence of mental disorder in such a country (in this instance, the Philippines) is truly low, or whether hospitalization is simply an infrequently used method of treatment. The forms of behavior considered pathological among Filipinos will be determined, and a study will be made of those that are treated in a hospital versus those that are managed in the community.

Schizophrenia in childhood

The fact that schizophrenic phenomena are manifest among the young is regarded by many investigators as potent evidence supporting the concept of schizophrenia as a dynamic developmental disorder. Childhood autistic behavior, for example, which is typified by a withdrawal from the world of reality, is viewed as the earliest form of schizophrenia. It is also the most poignant, for it is a portent of the waste and suffering of adult years to come.

In the treatment of childhood schizophrenia, the problem of drug therapy is a difficult one—for the differential application of drugs must be made carefully in terms of subtle differential diagnoses.

In order to get a trustworthy measure of a drug's effect on emotionally disturbed children, one investigator has found it necessary to divide such children into four general groups: (1) Severely impaired schizophrenic children; (2) a borderline group, less severely impaired; (3) children with predominantly neurotic manifestations—anxiety, and feelings of helpless dependence and inadequacy; and (4) children with predominantly sociopathic or paranoid features who tend to deny personal responsibility for their feelings and acts.

In a pilot study, most of the more severely disturbed children—those in groups 1 and 2—improved on chlorpromazine, a widely used tranquilizer; about half improved on another drug; none improved on a placebo treatment. Among the other children, however, the effectiveness of chlorpromazine—in terms of the percentage of children who improved—differed little from that of a placebo. Improvement in the first two groups, then, seems to depend primarily on the effectiveness of the drug being studied; in the second two groups, upon such factors as hospitalization, psychotherapy, and special education.

The grantee's research team has confirmed that a child's response to a psychiatric drug may be quite different from an adult's. For example, trifluoperazine, a tranquilizer having less sedative action than chlorpromazine, has been found to be a stimulating agent when given to retarded schizophrenic children and to be capable, on the basis of preliminary findings, of bringing moderate improvement. Other drugs are being tried in the hope that even more potent agents will be discovered.

The investigator estimates that at least 60 percent of severely disturbed children can be moderately improved by presently available drugs. Among children in an outpatient population who were too disturbed to benefit from psychotherapy, drugs enabled one-fourth to go to regular schools and another one-half to participate in group activities and special classes.

Special screening of drugs potentially valuable for disturbed children is essential. the grantee reports, because a drug's action may depend upon the stage of the child's development. Quite possibly, drugs that are ineffective in adult animals or human beings may prove valuable for children.

The investigators also point out that dosages of psychopharmacologic drugs must be determined separately for children and not merely adjusted from adult dosages according to body weight. A dosage that has been scaled down in this manner may be so high for a child as to cause toxic symptoms. Or, it may be so low as to be ineffective.

In another study, the aim is to see whether psychotic children who would ordinarily be referred to institutions can continue functioning in their own homes through the use of a tranquilizing drug. The plan is to study two groups of children over a 26-week period; one group will receive a tranquilizer in appropriate regular doses while the other group will receive a placebo.

Because the development of speech and language reflects so strongly various elements of personality, a fuller understanding of childhood schizophrenia is being sought by a number of investigators through the study of linguistic phenomena. In one project, for example, the primary object is to explore the language comprehension and speech behavior of a group of autistic children. Vocalizations and verbal output will be tape recorded in various situations for phonetic analysis, and language comprehension will be explored by means of a specially developed scale. In another project, the purpose is to investigate the verbal behavior of schizophrenics (adults as well as children) as contrasted with normal controls to determine the variables which underlie normal and abnormal speech. The results of the study may throw light not only on the psychodynamics of schizophrenic behavior, but they may also differentiate among children with good and poor prognoses.

Additional insights into potential for treatment and prevention are being sought through intensive studies of the relationship between the schizophrenic child and his parents. One investigator reports that, in his experience, each parent of a child with a disorder severe enough to be termed childhood schizophrenia manifests severe psychological conflicts prior to the development of the child's disorder. Often, without seeing the child. the investigator can predict from an initial interview with the parents the degree of psychopathology in the child.

Diagnosis, treatment, and prevention

The search for new and more effective techniques for the treatment of schizophrenia continues concurrently with attempts to understand its causes and to initiate methods of prevention. In the area of psychopharmacology, the past few years have seen a series of converging findings that demonstrate the effectiveness of potent phenothiazine drugs in the treatment of both acute and chronic schizophrenics. Studies conducted under NIMH grants have provided scientific support for the usefulness of drugs in returning patients to the community, and in reducing the chances of relapse and rehospitalization. Even the seriously ill, relapsing patient can avoid rehospitalization, results have shown, with a combination of phenothiazine drugs and a day-care program.

Much of the research recently completed or nearing completion in this area is concerned either with (*a*) finding improved means of classifying patients and predicting the outcome of their illness so that various forms of treatment, particularly drug therapy, can be more accurately evaluated, or (*b*) learning what factors enable former hospitalized patients to remain in the community.

In one project, the investigator is comparing two groups of 12- to 15-year-olds, the first identified as a high-risk group having one or both parents with a history of schizophrenia, and the second a low-risk group with neither parent having a history of psychiatric illness. This study is being carried out in Denmark because of its relative population stability and efficient medical recordkeeping methods. The long-range aim of the project is to study a group of normals, predict which of them will become schizophrenic, and wait a sufficient number of years to allow nature to test these predictions and to observe the circumstances surrounding the onset of the psychosis.

Another group of investigators with NIMH support has developed a prognostic index and is using it to predict for each schizophrenic patient in a drug-evaluation program the natural short-range course of his illness if untreated. Among the factors found to be associated with a favorable outcome are marriage, extroversion, good premorbid adjustment, sudden onset of illness, demonstrable precipitating factors (severe stress), and first attack, or a history of previous remission. Factors associated with a poor outcome include unmarried state, introversion, poor premorbid adjustment, onset of illness before 20, gradual onset of illness, no demonstrable precipitating factors, and duration of more than 2 years.

Frequently the patients did not present either pattern in pure form. More than 80 percent of the unimproved patients, however, had fewer than three favorable factors. Several patients went contrary to the general findings and are being studied further. One, as an extreme example, demonstrated all the unfavorable factors and yet appeared among the improved.

A patient's condition, the investigators report, cannot be determined accurately—at least for the short term—on the basis of whether or not he is still in the hospital. A number of schizophrenic patients in this study were found genuinely improved by the time of the first followup but remained in the hospital for lack of suitable homes or understanding families. An even larger group of patients were described as sheltered psychotics, able to be outside the hospital only through the support and tolerance of their environment.

Most of the patients remaining in the hospital, though well enough to leave, were from the upper social and economic group. The researchers suggest that this group is unwilling to have the patients at home unless they can take up a role judged to be in keeping with the family's status.

A new demonstration of the value of ataraxic drugs appears in the preliminary findings of a study that investigates the relative effectiveness in a State hospital setting of types of treatment in common use for schizophrenics.

First admission schizophrenic patients were assigned to one of several treatment groups—including individual psychotherapy, psychotherapy plus tranquilizing drugs (usually trifluoperazine), and tranquilizing drugs alone. A control group did not receive these types of treatment. The typical patient was in the late twenties, had gone through 11 grades of school, had had predominantly paranoid psychotic symptoms for an average of 23 weeks, and was not entering the hospital voluntarily. Patients were excluded from the study if, at one extreme, they were already showing marked improvement during the initial evaluation period or if, at the other extreme, they were considered to have little chance of leaving the hospital in less than 2 years.

On the basis of preliminary observations (1) the use of trifluoperazine shortens hospital stay and increases the release rate without increasing the readmission rate; (2) individual psychotherapy alone does not shorten hospital stay or increase the release rate; (3) the combination of individual psychotherapy and drug treatment is possibly more effective than drugs alone in shortening hospital stay and increasing the release rate, but it may also increase the readmission rate. The study is continuing.

Striking evidence is now at hand that most patients who have been discharged from mental hospitals can function in the community—provided the community has a mental health center staffed to provide effective aftercare. The evidence appears in the report of a research team, supported in part by an NIMH grant, that kept 300 former State hospital patients under continuous close supervision for 5 years in New York City. The patients ranged in age from 17 to 71 years; about 25 percent were men. Schizophrenia had been diagnosed in about 80 percent, manic depressive, involutional and senile, and other psychoses in the rest. The research unit, part of a State aftercare clinic in New York, is staffed by two psychiatrists, two social workers, an occupational therapist, a nurse, and two clerical workers.

Some major findings:

(1) During the 5 years of the study, only 37 percent of the former mental hospital patients had to return to a hospital—whereas the overall average return rate of patients in New York City aftercare clinics is reported to be almost exactly the same during the first year alone. The low return rate for the patients in this study is assumed to reflect the use of tranquilizing drugs, plus supportive psychotherapy, and the general intensive followup care given by the research unit.

(2) Most patients continued to take a tranquilizer—chloropromazine—during the 5 years after leaving the hospital. No major side effects were observed. When patients dropped the medication, most of them had a recurrence of symptoms.

(3) Of the patients still in the community after 5 years, 40 percent were fully self-supporting, 13 percent were partially self-supporting, 12 percent were unemployed, and 35 percent were homemakers. The employed showed good job stability. The use of a tranquilizer did not interfere with work capacity, work performance, or learning ability; no accident-proneness was observed.

(4) Patients and relatives alike must be prepared for the patient's return to the community and for the need to continue drug therapy, possibly on an indefinite basis. Patients back in the community need increased reassurance, and often an adjustment of drug dosages, in times of stress, and this need continues a long time. Many former patients seem to benefit just from knowing that an agency stands ready to discuss their problems with them at any time.

A concept that may lead to considerable improvement in a community's ability to prevent mental illness is being explored by a team of investigators with the aid of a special NIMH grant. This concept holds that mental illness—in many cases at least—is related to such ordinary crises of life as getting married, changing jobs, having a baby, losing a loved one. The way a person handles a particular crisis may strengthen his mental health and leave him better able to cope with the next crisis. Or it may increase his vulnerability to, and even bring on, mental illness. By observing how people cope with the danger and frustration of stressful events, this concept holds, it should be possible to say which types of coping behavior lead to a healthy mental outcome and which do not. Then it should be possible to use these findings to recognize—early enough to help—the people who are heading toward trouble.

Under this concept the findings would be applied not only by the relatively few psychiatrists and psychologists but also by all the other care-giving agents of the community, including nurses, clergymen, public health workers, and teachers. Preventive psychiatry thus would be practiced on a communitywide basis.

Descriptive studies

Despite the considerable advances being made in the diagnosis and treatment of schizophrenia, many scientists today are still at the first, rudimentary level of inquiry—the phenomenological level—in their attempts to describe with more precision the aberrations of schizophrenia. It is important to note, however, that with increased research sophistication and with steadily increasing funds of knowledge, descriptive data are becoming more rigorous and more immediately usable for purposes of understanding the etiology of schizophrenia and of initiating measures of prevention and treatment.

Three examples, taken from many comparable studies, follow:

(1) One investigator has sought to describe and analyze the schizophrenic's social behavior in the hospital ward and how the hospital staff responds to that behavior. Recent findings suggest that the quality of the ward as a social system contributes to the perpetuation of chronicity in mental illness. It was observed, for example, that episodes of psychotic behavior are correlated with the nature of preceding interactions with the staff; psychotic behavior is exacerbated when

the patient is treated as an object rather than as a person with feelings, needs, and rights. Such treatment continued over months and years must have a corrosive effect.

(2) In another study, the emphasis is on the more private, psychological functioning of the patient—specifically, his dream. Freudian theory states that dreaming acts like a safety valve because it permits the symbolic expression in nighttime hallucinations of drives that an individual represses while awake. A research team supported by NIMH hypothesized that a borderline schizophrenic patient might show increased dreaming because of intensified drive pressure. As the pressure mounted and as the individual's drive-restraining forces disintegrated, at a certain point he would be dreaming while he was awake; that is, he would be psychotic. The team's preliminary findings are consistent with this hypothesis. Five borderline, potentially schizophrenic patients, ranging in age between 22 and 26, had dream periods that averaged 26.5 percent of a night's sleep. The dream periods of normal control subjects, on the other hand, averaged 19.8 percent. Investigators in the NIMH intramural program have corroborated these findings and are collecting data on a number of other aspects of the sleep-dream cycle in schizophrenics. Current efforts are focused on the effects of drugs on dream patterns.

(3) In yet other study, an investigator is focusing on the cognitive functioning of schizophrenics. He is seeking evidence on how schizophrenic thinking differs from that of either normal, brain-damaged or mentally defective subjects. He wants, too, to find whether the schizophrenic thinking disorders fall into patterns that can be related to other symptomatology.

Methodological studies

Behavioral scientists engaged in research on schizophrenia continue to use those research techniques, analytic methods, and psychological tests and measurements available to them. At the same time, however, a number of investigators are attempting to sharpen existing methodological approaches, and to add to the arsenal of research weapons available in the field.

One research team, for example, is looking into a new method for analyzing electroencephalographic data by using an analog-signal correlator to obtain statistical measurements of the similarity between recorded signals; initial work in this area has provided measurements which appear to differentiate between normal and schizophrenic patients. Another scientist is investigating the problem of psychological measurements among schizophrenics; he is studying the reliability of rating scales in long-term assessments of chronic schizophrenic patients in order to provide researchers with more precise tests of patient behavior.

RESEARCH UTILIZATION BRANCH PROGRAM

The Research Utilization Branch effort in schizophrenia is guided by its role in linking the findings of the research laboratory, field demonstrations and pilot projects with those agencies and groups responsible for developing and conducting mental health programs and services. Staff and program resources are devoted to a dual effort: the stimulation of research and field trials of improved patient treatment, care, and rehabilitation and the dissemination and translation of research findings and clinical practice into operating programs.

In the mental health project grant program, about one out of every three projects supported is concerned to some extent with the problems of the treatment and rehabilitation of schizophrenics. Support was provided in 1963 for the National Day Hospital Workshop attended by about 300 participants from the States and abroad. A national meeting of Halfway House staff and a regional conference on aftercare were also held. New intensive treatment hospital programs are being tested in such places as Washington State and Pennsylvania, Massachusetts and Ohio. Homemaker services are being provided to the families of hospitalized mothers in Indiana. A number of hospitals are experimenting with the increased therapeutic role of ward and nursing staff in the total treatment program.

Since the major objective of psychiatric treatment is to prevent prolonged hospitalization and to restore patients to productive community life, projects are being supported which demonstrate the effectiveness of paid work as therapy and integrate vocational rehabilitation programs into hospitals.

Two special staff studies are underway to evaluate and integrate research endeavors in improved patient care. One is observing successful hospital treatment programs and mental health project grants demonstration projects to find out how innovations in patient care or administration are implemented and sustained. One of the major problems facing State hospitals is the management of chronic patients. The branch is also involved, therefore, in a systematic study of the various approaches to the rehabilitation of chronic patients in State hospitals. The findings of both these studies will be available for use in consultation by staff to hospitals planning modifications in therapy and administration, or who are planning projects under the extension of the title V program by the 88th Congress.

The concept of continuity of care—from diagnosis to rehabilitation—is the basic framework within which Branch activities operate. There has been a growing trend toward retaining the mental patient in the community for treatment. This reflects supportive evidence coming from the increasing number of community psychiatric resources and from a number of research and demonstration projects. The evidence is that many forms and degrees of mental illness can be treated and disability prevented effectively and economically through community services for prevention, diagnosis, treatment, and rehabilitation. Mental health project grant funds are, therefore, supporting a wide variety of experimental therapeutic programs in the hospital-community continuum of care. These include psychiatric units in general hospitals; emergency services; home treatment programs; preadmission services; aftercare programs in cooperation with outpatient clinics, family agencies, and health departments; family and foster care services; day hosiptals as alternatives to hospitalization and as posthospitalization facilities; halfway houses, ex-patient therapeutic social clubs; services to families of hospitalized patients; volunteers as part of psychiatric rehabilitation programs; sheltered workshops, and other psychiatric rehabilitation services.

Marked successes in home-care programs are reported by several Institute-supported investigators. In New York City, nearly two-thirds of 200 randomly selected psychiatric patients were successfully treated on a strictly day care basis in a special community center. Many of these patients, treated from 9 a.m. to 4 p.m. daily, 5 days a week, were able to resume normal activities much sooner than with traditional full-time hospitalization—in some instances for the first time in many years. Average duration of full-time treatment was 6 weeks, with three and a half months the longest single instance of continuous therapy. The investigators say their observations (*a*) indicate a need for sharp reappraisal of traditional methods of hospitalization of the seriously mentally ill and (*b*) lend support to the concept of community-based physchiatric hospitals.

An additional significant program mechanism used to encourage the development and improvement of treatment programs for schizophrenics is the technical assistance project. Among the workshops held in 1963 by a State or group of States in cooperation with NIMH were TAP's on the following subjects: (1) An evaluation of the unit system of care of a large State mental hospital; (2) dental care as an integral part of progressive treatment programs in institutions; (3) improvement of staff relationships in a mental hospital; (4) program planning for volunteer services; (5) the role of the settlement house and the community center in providing services to the mental patient; (6) the community social club and the returning mental patient; (7) planning better services for emotionally disturbed children of school age. An important byproduct of these projects is that they not only provide opportunities for research utilization, but through the exchange of ideas, knowledge, and experiences often stimulate new research demonstration and pilot projects.

BIOMETRICS PROGRAM

As part of its total program, the Biometrics Branch is engaged in measuring the prevalence and incidence of mental disorders, and relating this information to pertinent factors of demography, sociocultural environment, and treatment programs. Along with this function, the Institute's biometrics program provides consultative and direct services to State and local departments of mental health. The Branch also supports a long-range program to improve and coordinate the flow of statistical data from various sources in the United States.

The expansion of the newer treatment methods—including day, night, and open hospitals, and the use of drugs—has led to increased complexities in the interpretation of statistical data, and has emphasized the need for new statistical reporting systems of adequate scope and flexibility. A model reporting area, in which mental health statistics are processed each month, now includes 33 States.

Cohort studies of the fate of schizophrenic admissions, among other patients, have shown wide interstate variations in release, retention, and death rates, as a function of hospital policies. Through a refinement of cohort studies, Branch staff members are now attempting to control some of the variables which previously made the comparability of such data difficult or impossible.

Through the national reporting program on outpatient psychiatric clinics, data are also available on services to schizophrenic outpatients. It is estimated that approximately 5,000 patients under 18 years of age (7 per 100,000 population) and 39,000 patients 18 years of age and over (34 per 100,000 population) discharged from the 1,589 clinics in the United States in 1961 were diagnosed as schizophrenics. This represents only 5 percent of the patients under 18, but 23 percent of the patients 18 and over diagnosed with a mental disorder. Among the schizophrenic patients resident in the public mental hospitals in 1961 (half of the total resident population), the median age was 51 years as compared with 61 years for all other resident patients; almost half of the schizophrenic resident patients were age 45 to 64 years.

Not only are biometric data of the kinds noted here of importance in sensing the distribution and flow of types of mental disorder under various conditions, but it is probable that comparative data will further the refinement and standardization of present day clinical, diagnostic techniques.

TRAINING

The Institute's support for the training of professional personnel in skills relevant to schizophrenia is an integral part of the training grant program in psychiatry, psychology, biological and social sciences, social work, and nursing. In addition, a large share of the Institute fellowship program supports the training of scientists in research skills associated with the understanding and treatment of schizophrenia. Predoctoral and postdoctoral fellowship programs supporting basic training in mental health research have been amplified in recent years by fellowship programs supporting higher levels of research training, to help establish stable research positions, and to meet specific research training needs in various problem areas like schizophrenia.

SUMMARY

The studies cited in this summary of current work on the problem of schizophrenia are intended as an illustrative rather than an exhaustive representation of the program.

While most of the studies are quite clearly related to specific schizophrenic phenomena, the eventual understanding of a complex disorder such as schizophrenia depends not only on exhaustive exploration of the schizophrenic process itself, but, more important, on an accumulation of knowledge regarding the fundamental mechanisms involved in the brain and in behavior.

The causes of schizophrenia are still unknown. The pathogenesis of the disorder undoubtedly involves complex interrelationships within the nervous system, and interactions among the nervous system, various other organ systems of the body, and the interpersonal relationships of individuals. Basic information from a variety of sciences is, therefore, of prime importance. Basic research on normal thought processes, for example, is essential to an understanding of abnormal thinking. Fundamental knowledge of normal metabolism and of the biochemistry of the brain is essential for comprehension of the ways in which these processes may be defective in a disorder like schizophrenia.

It can be stated with some confidence that when the final chapter in man's understanding of schizophrenia is written, the great bulk of the contributions which will have led to that achievement will have come from basic research of the type noted above—work which is in fact research in schizophrenia, even though it cannot be designated as such at this time by the scientists themselves or by anyone reviewing their efforts.

There are no assurances on the basis of current research that the schizophrenic illnesses which have challenged the best scientific minds for 2,000 years will be solved within the next year or two. There are, however, a gratifying number of new and interesting observations of considerable potential significance which demand further exploration. Fortunately, an increasing number of competent investigators are interested in exploring them.

PROPOSAL FOR SEPARATE ORGANIZATION ON SCHIZOPHRENIA

Mr. FOGARTY. Briefly tell us about some of it.

First, I received a letter from the Palo Alto Medical Research Foundation, Palo Alto, Calif., signed by Dr. Jackson, in which he said:

> Dr. Leo Bellak wrote me concerning his interest in the establishment of an organization which would be devoted to research in schizophrenia, one of the most pressing mental problems. I think this would be a very useful organization, specially if it would have a civilian board that would remove it from the immediate problems involved in Government-run operations.

Do you care to comment on this suggestion?

Dr. FELIX. I am aware of this recommendation. Some of my colleagues who were written about this have told me.

I would point out that, since 1948, something over $50 million, nearly $60 million of the appropriations for research alone made to the NIH have gone for research in the area of schizophrenia. In this year of 1964, $14.75 million of our money is going for work in the area of schizophrenia.

I do not believe that one can study schizophrenia as an isolated entity without taking into account other kinds of mental illnesses and causes of them, any more than one could consider smallpox as an isolated entity without taking into account other kinds of infectious diseases and some of the basic factors of immunity, and so forth, which might be part of the problem in dealing with such a condition.

I would be most vigorously opposed to the setting up of some subinstitutes by categories of mental illness because I believe you scatter your energies, you diversify your attention so that some of the more basic problems which underlie them all cannot be properly dealt with.

DRUG ADDICTION

Mr. FOGARTY. What about progress in the problem of drug addiction?

What about the population of Lexington?

Dr. FELIX. The Bureau of Narcotics has put out some charts and graphs on the number of addicts by various categories which, if the committee feels would be helpful, I can submit for the record.

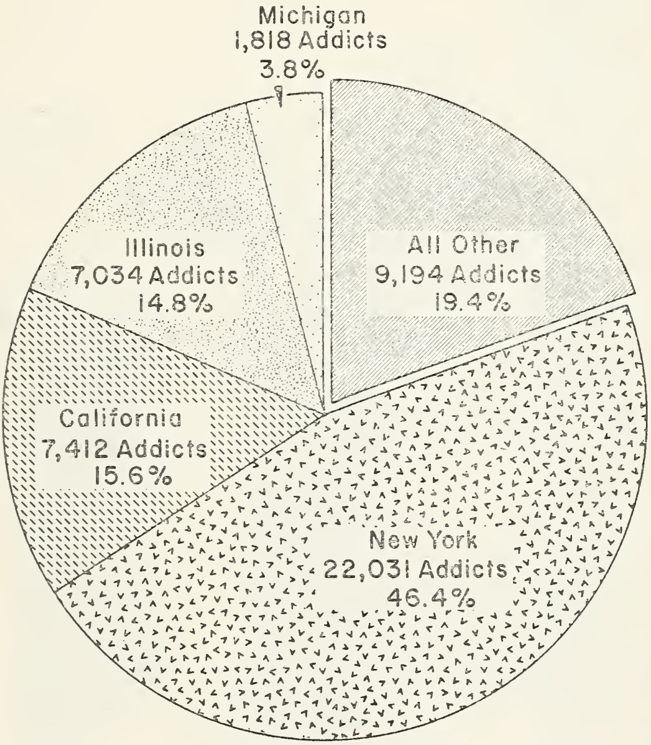
Mr. FOGARTY. Put it in the record.

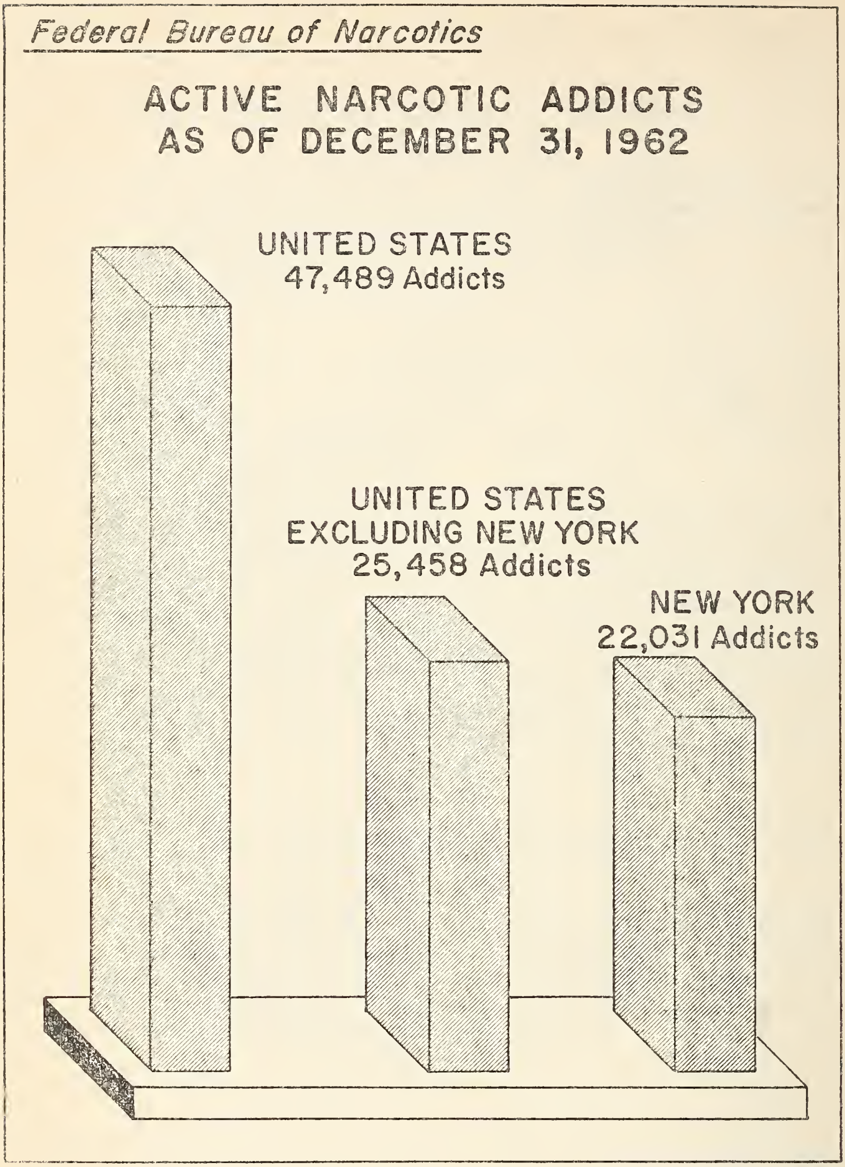
(The material referred to follows:)

Federal Bureau of Narcotics

ACTIVE NARCOTIC ADDICTS
REPORTED IN
SEVERAL SELECTED STATES
AS OF DECEMBER 31, 1962

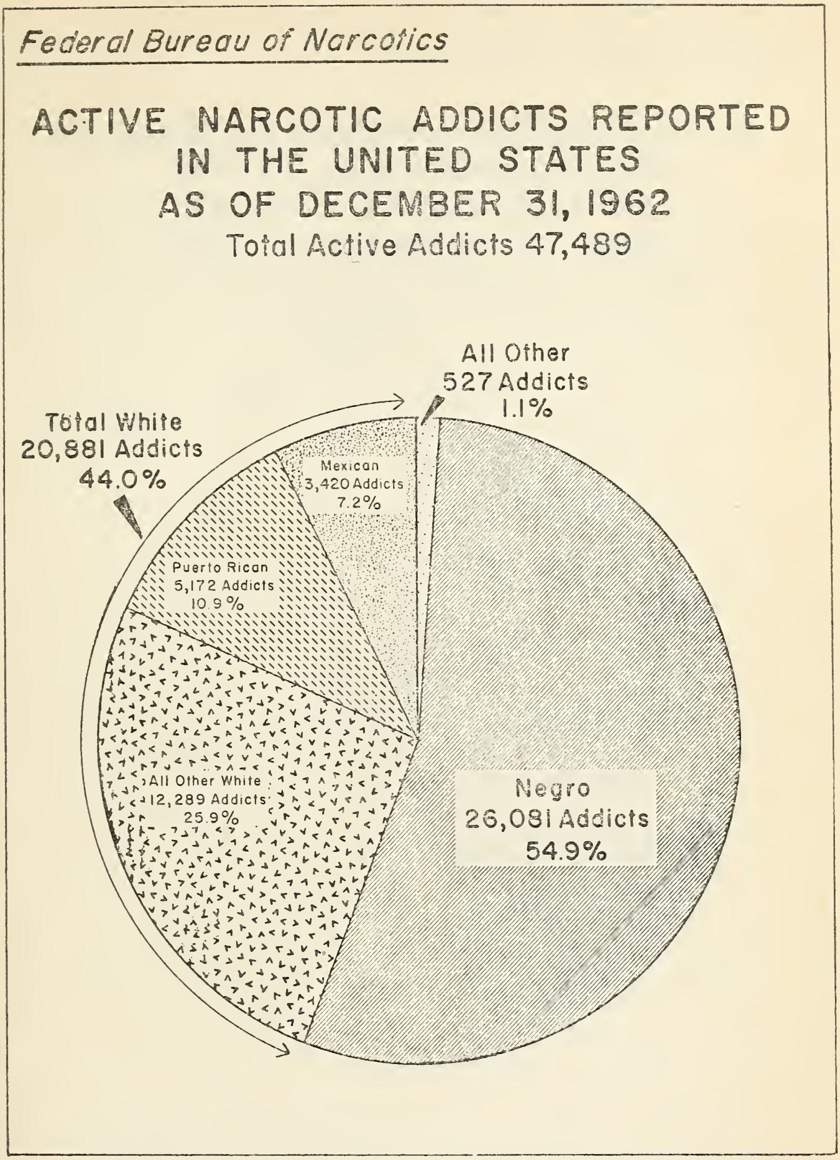
Total Active Addicts 47,489





Federal Bureau of Narcotics

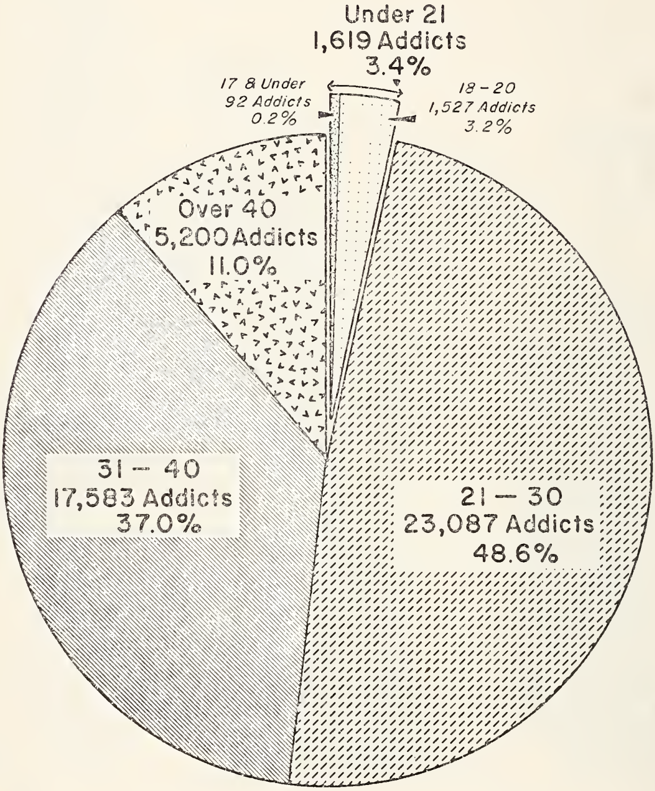
ACTIVE NARCOTIC ADDICTS AS OF DECEMBER 31, 1962



Federal Bureau of Narcotics

ACTIVE NARCOTIC ADDICTS REPORTED IN THE UNITED STATES AS OF DECEMBER 31, 1962

Total Active Addicts 47,489

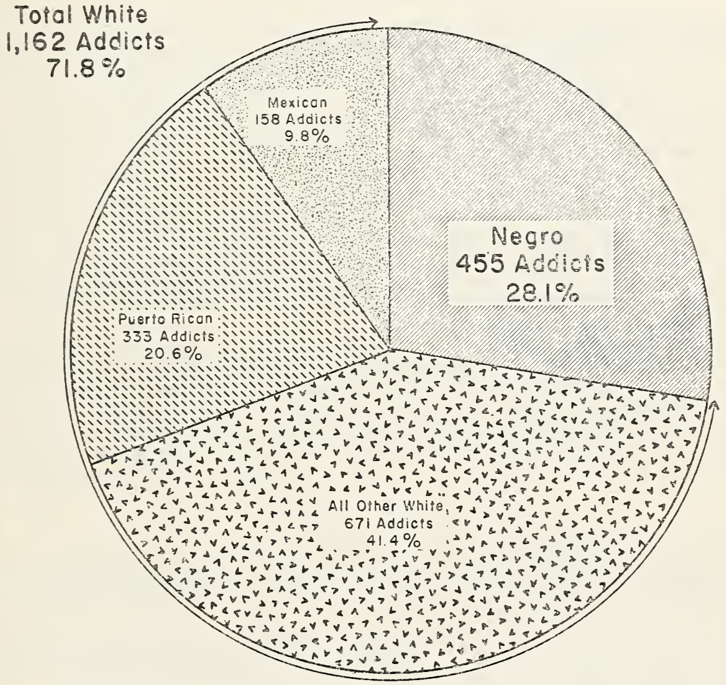


Federal Bureau of Narcotics

AGE OF ACTIVE NARCOTIC ADDICTS
AS OF DECEMBER 31, 1962
IN THE UNITED STATES
Total Active Addicts 47,489

Federal Bureau of Narcotics

ACTIVE NARCOTIC ADDICTS
IN THE UNITED STATES
UNDER 21 YEARS OF AGE
AS OF DECEMBER 31, 1962
Total Active Addicts Under 21 — 1,619



All Other Addicts - 2 (0.1%)

SPECIAL REPORT—DRUG ADDICTION

National Institute of Mental Health activities in drug addiction range from basic inquiries into the possible addicting qualities of new drugs to the promotion of State and local program development concerning drug addiction. Work is carried on through technical assistance and consultation services, mental health project and research grants, intramural research and in other ways.

Drug addiction is apparently a result of physical, psychological, social, and other factors which influence the person's development at a crucial time in his life. Although there is progress, more information is needed to understand how addiction develops. Further research is needed on the basic mechanism of drug action, on the effectiveness of different therapeutic approaches and methods, on the life history of addicts and the impact of various sociocultural factors upon them.

When considering treatment and rehabilitation, it is becoming more evident that addiction should be viewed as a chronic, often intermittent, illness needing followup services in the community after hospitalization.

NIMH-SUPPORTED DEMONSTRATIONS

The New York demonstration center, established in 1957 through Institute support, ended in 1962 and a final report upon its work has been published. The center was a demonstration project in which selected patients discharged from the U.S. Public Health Service Hospital in Lexington, Ky., were referred to appropriate community agencies. Almost all of the New York City agencies approached agreed to extend services to referred patients. At times this required a revision of policy. The report underscores the importance of working with the family environment of the addict and the need for integrated, long-term community programs and services to provide support to the returned addict.

A major contribution of the project was the mustering for the first time of many community services for the addict, and channeling him to them. Many patients participated with some regularity and continuity in a treatment program. Gradually some showed improved general functioning in the areas of employment, socialization, an increase in drive to overcome addiction, and an increase in the intervals of abstinence.

Experience from this project is being used in a second 5-year demonstration based on a contract with the Medical and Health Research Association of New York City, Inc. It is being conducted in Washington Heights with collaboration of the New York City Department of Health and the New York City Community Mental Health Board. Public health nurses, social workers, and other staff at the Washington Heights Rehabilitation Center will provide treatment and aftercare for addicts, assess community needs and study effective rehabilitation techniques.

STATE AND LOCAL PROGRAMS

Some examples of activity at State and local levels follow.

California has developed the former Corona Naval Hospital near Los Angeles into a rehabilitation center having treatment facilities for approximately 2,300 addicts.

The Colorado Department of Parole has initiated some group counseling for addicts in the State prison. In addition, a new followup procedure for paroled addicts involves the use of thin-layer chromatography for faster and more effective detection of opiates in the urine.

In New York the Metcalf-Volker law went into effect on January 1, 1963. It provides for civil commitment to State hospitals for detoxification and aftercare of arrested narcotic addicts and for the voluntary admission of nonarrested ones. There is provision also for establishing special facilities for those under the age of 21, as well as for a research and training program. In New York City, 290 beds operated by its department of hospitals were available to addicts seeking hospitalization voluntarily. The New York City Department of Health is operating four rehabilitation centers.

Massachusetts legislation provides for establishment of a drug addiction rehabilitation program in the State department of public health to be administered by a "drug addiction rehabilitation board." It is to be composed of the commissioners of mental health, correction, and public health or their designees. The program to be administered by the board will be in but not under the control of the department of public health. Funds for addiction programs will be requested through the health department. There was enacted also a "drug addiction rehabilitation law." It includes provision for civil and court commitment procedures, for release of civilly committed patients, for establishment of rehabilitation centers, for outpatient care, and for care and treatment on probation and on parole.

In Puerto Rico, a drug addiction research center is located at its psychiatric hospital. The center began and continues to function primarily as an outpatient service for drug addicts. A variety of services, including a day hospital, are also provided.

INTRAMURAL RESEARCH

The NIMH Addiction Research Center, located at the U.S. Public Health Service Hospital in Lexington, Ky., is conducting research in the pharmacological, neurophysiological, biochemical, psychological, and socioeconomic aspects of drug addiction.

A large part of the Center's research is devoted to the prevention of drug addiction. This work is essentially of three types: (1) Assessing narcotic analgesics and other types of drugs for their abuse liability; (2) assessing factors that predispose certain individuals and certain segments of our society to drug abuse; and (3) providing tools that will assist in the identification of drug addicts and abusers.

A second major area of research is the identification and description of pathophysiological processes that result from drug addiction and abuse, and the relationship of these processes to continued drug use and to relapse.

Finally, the research program is aimed at a large number of basic questions—learning how drugs such as morphine, barbiturates, and LSD act at the molecular tissue and system levels, how anxiety can be experimentally defined and measured and what biological changes are responsible for tolerance and physical dependence.

New analgesics are being investigated for addictiveness, not only to learn their addiction liability and to find effective analgesics that are nonaddicting, but to gain insight into the mechanisms of tolerance and physical dependence. During the year, a number of agents with low addiction liability were examined.

The agents include two indane derivatives reported to be as potent as codine as analgesics, a congener of chlorpromazine (methotrimeprazine) which also has significant analgesic properties, and two phenazocine derivatives that resemble nalorphine. One of these phenazocine derivatives, 2-hydroxy-5,9-dimethyl-2-(3,3-dimethyl)-6,7-benzomorphan (II–C–2), which has been characterized as a weak morphine antagonist in animals and which is approximately one-half as potent as morphine as an analgesic in man, is relatively ineffective in inducing morphinelike subjective effects in therapeutic doses and produces only a relatively low degree of physical dependence. In man it was ineffective in both suppressing and precipitating abstinence.

Study of another analgesic, II–C–3 (2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan) indicates that it is a most exciting agent, both from a therapeutic and a theoretical point of view. It is reported to be approximately 40 times as potent as morphine as an analgesic and is approximately 10 to 20 times as potent as morphine in producing morphine like euphoria. When administered to subjects who are physically dependent on morphine, it precipitates a violent abstinence syndrome. Although final assessment of this agent cannot be made now, a very low addiction liability appears likely and it may be a useful potent analgesic. The fact that II–C–3 produces a type of physical dependence is of great theoretical importance, especially in view of the fact that it is a morphine antagonist and that patients do not seek this agent or other narcotics when being withdrawn from it.

It has been thought that one of the basic personality defects that may predispose certain individuals to narcotic abuse is their intolerance to anxiety, that they may have many sources of anxiety, and that they seek morphine for its anxiety-relieving properties. Evidence to support this hypothesis has been obtained in man, in a study using conditioned anxiety in which a tone has been paired with an anxiety-producing stimulus; i.e., electric shock. In the study, it was noted that during the conditioning procedure, resistance of the skin fell, indicating increased sympathetic nervous system activity and anxiety and that discrete phasic decreases in resistance could be produced both by the shock and by the conditioned stimulus, tone. It was of great interest that morphine antagonized the tonic decrease in skin resistance to discrete conditioned (tone) and unconditioned (electroshock) stimuli.

A new method for rapid effective extraction of a wide variety of opiate and opioid drugs from urine has been developed, permitting identification of these agents, without hydrolysis, through a combination of thin-layed chromatography, gas chromatography, and spectrophotometric methods.

The social science section of the Addiction Research Center was established recently and is acquiring a large volume of data from records of the hospitals in Fort Worth, Tex., and Lexington, Ky., and from two followup studies involving addicts in Kentucky and in Puerto Rico. These projects will provide information concerning social, economic, and cultural factors contributing to drug abuse.

Recent studies of morphine addiction in the rat have provided experimental evidence in two areas of possible importance in understanding relapse to narcotics after treatment. It has been established that one sign of abstinence in the rat is the "wet dog" shake, so named because it resembles a dog shaking off water. This sign of abstinence has been shown to be conditionable by allowing rats to become abstinent in a linear maze. When these rats are withdrawn for many months from morphine and returned to a linear maze, an increased number of "wet dog" shakes are observed. If the rats have not experienced abstinence in a linear maze such a result is not found. The abstinence syndrome in the rat was divisible into two phases: an early or "primary" phase lasting about 1 week and a "secondary" one appearing after the first week and lasting for months. The later is characterized by an increased metabolic rate, increased body temperature, a tendency to be slightly more alert and active, an increased consumption of water, and an increased number of "wet dog" shakes. Rats show small but consistent abnormalities for at least 6 months following withdrawal from morphine. These results suggest the possibility that patients who have become addicted to narcotic analgesics may have long persisting abnormalities of several types: (1) a learned or conditioned type of abstinence, and (2) a slowly reversible or irreversible change in their physiological status.

A number of activities at the Center are in areas of basic research, aimed at solving or obtaining information about fundamental processes concerned with functioning of the brain, the development of personality, and certain types of phychic abnormalities. To gain further understanding about the mechanisms responsible for production of physical dependence to opiates, a rather extensive study of the sympathomimetic amines has been made.

Two agents, oxyaminoacetic acid and hydrazine, that are known to increase brain levels of gamma aminobutyric acid decrease the incidence of withdrawal convulsions in barbiturate-addicted animals. This finding is of particular importance because that acid has been proposed as a naturally occurring agent that inhibits or depresses the irritability of certain nerve cells. It suggests the possibility that barbiturate addiction may depress the synthesis of gamma aminobutyric acid.

The extensive program of clinical psychology research continues. It is aimed at discovering differences in behavioral attributes and personality that may exist between narcotic and alcoholic addicts and nonaddicts as well as to relate such differences to subjective effects of drugs. In these studies subjective reports have been assessed, under drug and no-drug conditions, using the Addiction Research Center Inventory (ARCI), a 550-item questionnaire developed for measuring drug-produced changes in mood, sensation, perception, attitudes, and needs. Recently a general drug-effect scale has been developed which is affected by all drugs studied so far. It has been found that postaddicts, under the effects of drugs and schizophrenics score high on this scale. It has been found also that alcohol and phenobarbital increase hostility and a tendency to overgeneralize.

EXTRAMURAL RESEARCH

Nine mental health project grants related to drug addiction were active during the year. The two projects to aid in program development and one for conference support were each for 1 year. A project in East Los Angeles assists the demonstration and evaluation of a halfway house for paroled narcotic offenders and is related to the California Department of Corrections program. Another project is aiding the group thereapy and probation supervision program, including a halfway house, of the Kings County Probation Department, Supreme Court of the State of New York.

Work proceeded under 24 research grants categorized under drug addiction or addiction plus another area. The grants aid a broad research approach to addiction with studies such as: dependence on narcotics in primates, the biochemical basis of narcotics addiction, posthospital study of addicts, a study of methods of determining narcotic usage.

TRAINING AND EDUCATION

The Institute provides support for graduate training in a number of mental health professions—psychiatry, psychology, social work, and nursing. The field of narcotic addiction has one specific training grant specific to it through which casework students receive field placement in a hospital treatment program for addicts. The Public Health Service hospitals in Fort Worth and Lexington, and the NIMH Addiction Research Center provide training in clinical care and research for psychiatrists and other medical personnel, nurses, psychologists, chaplains, and students. Both institutions provide assistance and counsel to visitors from the United States and abroad who come seeking help in developing their own programs in drug addition.

PROFESSIONAL AND TECHNICAL ASSISTANCE

Increased technical assistance and consultation about narcotic addiction was provided during the year. Much of this pertained to the development of mental health project grant application. The first technical assistance project pertaining to narcotic addiction was held recently in Massachusetts. Its report, "Perspectives on Narcotics Addiction," will receive selected distribution.

PUBLICATIONS

During the year, three new publications became available and can be purchased from the Superintendent of Documents, Government Printing Office.

Mental Health Monograph 2, "Narcotic Drug Addiction," PHS Publication No. 1021, presents information about the nature of addiction and is primarily for professional personnel. Mental Health Monograph 3, "Rehabilitation in Drug Addiction," PHS Publication No. 1013, is the final report on the New York Demonstration Center. "Narcotic Drug Addiction Problems," PHS Publication No. 1050, is a 212-page book on the proceedings of a symposium on the history of narcotic addiction problems which was held in March 1958 at the National Institutes of Health. Proceedings of the September 1962 White House Conference on Narcotic and Drug Abuse became available and have received wide distribution. The President's Advisory Commission on Narcotic and Drug Abuse issued an interim report in April 1963 and its final report is in preparation.

Dr. FELIX. You might be interested in some of the facts.

PRETTYMAN COMMISSION

Mr. FOGARTY. Before we get into this, were there some recommendations made on this problem recently by some Government agency or legislative committee?

Dr. FELIX. Yes, sir; this is the so-called Prettyman Commission. Judge Prettyman headed a commission.

I will be glad to tell you a little about that, too.

Mr. FOGARTY. Tell us something about it.

Dr. FELIX. This Commission, appointed as a special Presidential Commission held hearings and interviewed a large number of people and submitted a report last month. I believe I can supply the members of the committee with copies of this report if they wish it. It is a rather large one, you would not want it in the record, I know it must be 150 pages, but it has a lot of material, some of the members might be interested in.

In regard to the recommendations of the Commission, I will be brief. I am giving you these as I recall them, without comment because the Department has been requested by the White House to comment upon this. There will, I believe, be a departmental comment. Each of us will supply our own parts of this. Ours is being written, I have not yet seen it. I have been preparing for these hearings. So I do not know even what the position of my own staff would be on some aspects of this, although I strongly suspect I can guess. But I am in no position to give any opinion as to what the Public Health Service's position will be, let alone the Department's.

The recommendations I will give you: It is recommended that there be a special assistant to the President for narcotic addiction. It is recommended that there be a professional and citizens advisory board to this special assistant and to the President, that there be a Federal scientific council which will draw up a master plan and timetables, the amount of money to be spent, the direction in which these efforts should go, what emphasis should be given to what and for how long.

It is recommended that all the enforcement aspects of the narcotic problem be transferred to the Department of Justice, as for instance the Narcotics Bureau. It is recommended that all the regulatory functions concerned with narcotics, the amounts of drugs needed if you need to import, what kind of drugs are good for what, what are addicting, what are not, when should a drug be declared addicting, and when not; these functions be assigned to the Department of Health, Education, and Welfare.

There is one that I cannot quite understand, I am afraid my bias is showing through on this one, and I do not—well, if it does, I can only do what I can do, I am human, but there is a recommendation here that there be provided by legislation a civil commitment for addicts convicted of—for addicted people convicted of Federal narcotic offenses. I will not comment on anything else, but for the life of me, I do not see how you can make a civil commitment for a criminal case, No. 1. No. 2, I do not see why in the name of heaven you have to have a criminal record in order to have a civil commitment for this.

Mr. DENTON. You do for mental illness.

Dr. FELIX. In the old days in some States.

Mr. DENTON. You do now.

Dr. FELIX. I know what you are are talking about. Yes, I remember back in Colorado, when I was a young fellow——

Mr. DENTON. When a man is declared mentally ill, you put him in a hospital if it is dangerous for him to be at large.

Dr. FELIX. Yes. I remember when a person was served a warrant, he was charged with being a lunatic. The sheriff had to put it in his hand, even though he did not know what he was getting, he clamped it in his hand and took it away from him again. We have gotten away from this thing.

If narcotic addiction is a sickness—and it is a sickness, psychological and physiological—I do not know why you make it a crime.

To continue, it is recommended there be no more voluntary admissions to the Lexington or Fort Worth hospitals except for research purposes.

Is that correct?

Dr. YOLLES. Yes.

Dr. FELIX. It is recommended that there be money especially earmarked for research in drug addiction, appropriated money. This would apply to—this would be your concern, of course.

It is recommended that there be set up specialized treatment centers for addicts in certain critical parts of the country, that there be more funds appropriated for technical and financial assistance to the States that need it; that there be entered into certain international agreements, and I am not sure of the nature of these, with regard to narcotics control.

Now, those are the principal recommendations. You asked about addicts. According to the Narcotics Bureau——

Mr. FOGARTY. Let us stay with these recommendations now.

Dr. FELIX. Yes, sir.

EVALUATION OF COMMISSION'S RECOMMENDATION

Mr. FOGARTY. With the exception of one, you do not find too much fault with the others, do you?

Dr. FELIX. I do not want to give that impression at all. I have only commented on one.

Mr. FOGARTY. I did not say you were for them; I said you only found fault with one.

What other ones are you not happy about?

Dr. FELIX. I am not sure what the Department's position is.

Mr. FOGARTY. Never mind the Department. I am asking you now.

Dr. FELIX. I have to live with the Department.

Mr. FOGARTY. I am not talking about the Department.

Dr. FELIX. All right. I would wonder about the wisdom of placing all of these regulatory functions in the Department of Health, Education, and Welfare. I imagine this would mean Food and Drug. That poor organization is going to have its back broken with so many things to do. They get things so unpopular nobody else wants them, it looks like. My heart bleeds for them. I do not see why these have to be there.

I certainly am opposed to elimination of voluntary admissions to these hospitals. I cannot agree for a minute that just——

Mr. FOGARTY. What was the reason behind that?

Dr. FELIX. Because so many of them return. The recovery rate is low.

All right. This may well be. But I think we should go further into some of the studies we have done in New York and elsewhere as to why this may be low. It is not because they voluntarily go there. You know, if you just keep the church door open, sinners will come and go, but every once in a while somebody gets converted and does not sin any more. And Heaven rejoices more over one fallen person——

Mr. FOGARTY. I think we were given an example years ago about people working in the circus in the summertime and in the fall they go down——

Dr. FELIX. That is right. We have found in our study in New York and in Stamford, Conn., I believe it was, where they have set up special facilities for these people to be followed where they can get some close attention and followup, that they will, once they have gotten over their initial suspiciousness, that these people are not there to put the arm on them if they do something wrong, they will come voluntarily. An increasing number of these people are staying off of drugs.

One must also understand that narcotic addiction is a very complicated business. It is both habituation in the psychological sense, and it is addiction in the physiological sense from which a person apparently does not recover for from 6 to 9 months after he is taken off drugs, and there is a psychological problem in terms of the underlying personality difficulty.

Why we should take away the help of a voluntary admission, even though only 6 or 8 percent stay well after even two or three admissions, I do not know. As a physician, this is contrary to my basic moral philosophy, that after a person has had two or three trials at staying well from tuberculosis you throw him away because he ought to have better sense than to get sick again. I see very little difference, if one looks at it as a physician, between narcotic addiction and any other illness.

Mr. FOGARTY. All right. What are the other suggestions you do not see eye to eye with?

EARMARKED APPROPRIATIONS

Dr. FELIX. I have objections, but you would be the first to point out to me through your own initiative and what you have done, and so successfully done, Mr. Chairman, that you would not necessarily agree. You can rebut what I am going to say, but I am going to say it because I want it on the record.

I get very uncomfortable about significant sums of earmarked money for smaller and smaller pieces of activities. My hands are tied. I cannot roll with the punch. I cannot put my money where the opportunities are unless they are in a very narrow area.

Now, let me say, I will be the first to admit beginning about 1955 you began to push me real hard in the area of mental retardation. I did not like it. But there was nothing I could do about it. As a result of this, we opened up a whole new field. As a result of you, I think, more than any one person, we opened up a whole new field. I am grateful to you for it. I still do not like earmarked money.

Mr. FOGARTY. What about when we earmarked some money in the field of pharmacology in your institute?

Dr. FELIX. That is right.

Mr. FOGARTY. You did not like that either?

Dr. FELIX. I did not like that either, and we found a lot of things.

Mr. FOGARTY. That turned out pretty well; did it not?

Dr. FELIX. As I say, you can rebut me all over the map—I still do not like earmarked money.

Mr. FOGARTY. I do not think you have done very much in the field or narcotics. I think if we had earmarked a few million dollars more for research and special facilites this problem might be pretty well solved now. Your research carried on in Lexington is just a drop in the bucket. It never did amount to much, did it?

Dr. FELIX. You mean dollarwise?

Mr. FOGARTY. Yes.

Dr. FELIX. Scientifically, it amounted to an awful lot. Dollarwise, not as much as it should. It is running at a level of $570,000, that whole direct obligation——

Mr. FOGARTY. What was it 15 years ago?

Dr. FELIX. Oh, 15 years ago? I would have to—I will look that up and submit it for the record.

(The information follows:)

ADDICTION RESEARCH CENTER OBLIGATION

Fifteen years ago (1949) the Addiction Research Center had obligations of $78,605.

Mr. FOGARTY. I remember Mr. Keefe took a trip down there to the Lexington Hospital in 1947 or 1948.

Dr. FELIX. He called me back for half a day's special hearings after that. I have never gotten over the shock of that.

Mr. FOGARTY. You are spending $400,000 or $500,000 now; maybe you should be spending $3 or $4 million on this, because it is one of the most serious problems that could afflict the youth of our country; is it not?

Dr. FELIX. It is one of the worst. However, I point out between the ages of 18 and 20, according to the Narcotics Bureau, there are 1,619 such addicts in the United States. This is not a very large number.

I do not mean by this to——

Mr. FOGARTY Are most of them in New York City?

Dr. FELIX. I do not know.

There are four States in which all but 19 percent of the addicts are located: New York, 22,031 addicts, or 46 percent; California, 7,412 addicts, 15.6 percent; Illinois, 7,034 addicts, 14.5 percent; Michigan, 1,818 addicts, 3.8 percent; all others, 9,194, or 19.4 percent.

STAMFORD PROJECT

Mr. FOGARTY. Tell us about the Stamford project.

Dr. FELIX. It began in the summer of 1962. This is a title V project, the first one we made. It is sponsored by the Stamford Community Council. It involves research, education, and treatment of patients. Patients have been coming to the Center since the fall of 1962, both men and women, and they have come from every socioeconomic status, from rich to poor and high to low. The majority of the patients use heroin as a drug of choice. Many of them—some of them were individuals with a long history of drug use. Personnel of the Center feel the experience so far has shown that the users will come if they do not get suspicious and feel the police are going to be informed.

Of the original 65 which was the group followed here, 26 of them are imployed and the families are intact. Now, that is a lot better than our Lexington figures, where they are discharged from Kentucky and go to New York. Seventeen are in difficulty. The rest we do not know.

SYNANON PROGRAM

Mr. FOGARTY. There is another group in that area that a former Member of Congress wrote me about. This is a group, somewhere near Stamford, that has some success in alcoholism and narcotics.

Dr. FELIX. Synanon.

Mr. FOGARTY. That is right.

Dr. FELIX. Synanon.

Mr. FOGARTY. I understood that they have a very strict routine the patients have to adhere to. For those who could take it and stayed there, the results were pretty good. I think they made application for——

Dr. Felix. Yes, they applied. I think it was not approved, was it?

Dr. Yolles. That is correct.

Dr. Felix. It was not approved.

Mr. Fogarty. I have never seen the place; I have just heard about it from two or three people.

Dr. Felix. Synanon is a movement rather similar in the narcotic field to Alcoholics Anonymous in the alcoholic field. I believe it started in California, if I remember, in Santa Monica. The founder's name is Mr. Charles Dederich. There are two or three other chapters——

Dr. Yolles. One in Westport, Conn., one in Reno, Nev., one in San Diego, and a new one in San Francisco.

Dr. Felix. The former addicts live in, in these places, and their whole being is wrapped up in this effort to remain free of drugs. It is a very laudable activity. And the people are most sincere and energetic.

Now, I would like to go off the record.

Mr. Fogarty. All right.

(Discussion off the record.)

FATHER EGAN

Mr. Fogarty. I read in the paper recently about a person addicted being cured by some religious group in New York City. Do you know about that group?

The story was about how this young fellow went there and just completely stopped, and he claimed it was because of the atmosphere, the religious atmosphere.

Dr. Felix. Oh, I cannot think of his name.

Mr. Fogarty. In New York?

Dr. Felix. Yes; he is a Catholic priest. He is well known in the area. He has sort of a hostel for these people. He has been to my office. I am very impressed with the man's sincerity and his knowledge of narcotic addiction.

There was an article in some other magazine, like Reader's Digest or something—he sent me a reprint of it—about what he is doing. He is a bundle of energy. He is a short fellow, not much taller, or as tall as I am, but a bundle of energy and a very dedicated soul.

I can look this up and give you more information if you would like it in the record.

(The information referred to follows:)

Father Egan has worked very intensively in getting New York City hospitals to admit narcotic addicts. The Village Haven, Inc., a nonsectarian and nonprofit community agency, was formed to provide emergency, on-the-spot assistance to female addicts as they are discharged from prisons, hospitals, social agencies, etc. This agency has operated a clubroom-type facility which has aided over 400 female drug addicts.

Father Egan wishes to provide and operate a halfway house for female drug addicts, because the nonresident facility has not been adequate to meet individual needs for a residence, counseling, employment service, and a place to return when emergency help is needed.

ALCOHOLISM

Mr. Fogarty. Now, what about alcoholism? Are you making any headway?

This is another little earmarking we did a few years ago, if you remember. You were not doing hardly anything on this problem, so we earmarked some money one year.

Dr. Felix. I think I am going to believe I made a tactical blunder mentioning anything about earmarked money.

Mr. Fogarty. Did we not give you earmarked money for alcoholism a few years ago?

Dr. Felix. Yes, sir; you did.

MASSACHUSETTS PROJECT

Now, some new developments in the field of alcoholism, one very dramatic one carried on through a grant from us through our title V program at Massachusetts General Hospital in Boston. I have been interested in this and was very interested a week ago at a meeting of the Council on Mental Health of the American Medical Association, with the officials of all the State medical societies and their mental health committees. This project was described in a panel discussion as one of the finest examples of treatment of alcoholism.

The people at the Massachusetts General Hospital became concerned with the fact that alcoholic patients, for whatever reason, would come to its emergency ward—maybe a split scalp or acute alcoholic poisoning or delirium tremens or what not—they would receive whatever attention they needed for the presenting symptoms and that would be the last you would see of them. They never seemed to come back, they could not get hold of them.

They organized a team of a psychiatrist and psychiatric social worker whose full assignment was in the emergency ward. They made contact with the alcoholic patient when he came in, while he was on the stretcher, when he got out of the ambulance. They maintained contact with him, talking to him, making themselves available for all sorts of needs and demands such a person would have. They followed these people and where before practically nobody came for followup, 65 percent of these people—originally contacted through the emergency room—65 percent of these people came back for five or more visits as contrasted to 5 percent of the noncontacted group.

The project has had such an impact, a number of these people have remained off of alcohol. I say five visits or more. A number of these have had considerably more than five visits and remained dry.

This has attracted so much attention that this group is now serving as a consultant to another project, also on a grant from our Institute, in North Conway, N.H., where they are doing a similar study in a rural area. This has just started. We do not know what the results will be. We have no reason to think it will be any different.

Mr. Fogarty. Is this where a minister is interested in the problem?

Dr. Felix. Yes, sir. What is his name? Yes, sir.

Mr. Fogarty. I met him at a meeting in Boston.

Dr. Felix. He is an Episcopal clergyman.

Mr. Fogarty. Yes. He does quite a bit of work around this area.

OHIO STUDY

Dr. Felix. We are interested in the fact they have done a study of 3,000 alcoholics who have been admitted to Ohio hospitals. Eightythree percent of those admitted were male. This does not mean necessarily that this is an accurate reflection of distribution by male and female in the population, but they took care of the females other ways for a long time; they tolerate them, did something else. The males they sent to the hospital.

Mr. Fogarty. Many of the females stay at home.

Dr. Felix. That is correct. Yes, sir.

The nonwhite rate is two or three times that for the whites. This is nonwhite lumped together, everything, white and all other.

The most likely age for male first admissions for alcoholism in the Ohio State system is between 45 and 50 years of age.

Mr. Fogarty. What happens after 50?

Dr. Felix. After 50, it is not——

Mr. Fogarty. If you have not succumbed to it by that time, you are not likely to?

Dr. Felix. Either that or—there is something funny about alcoholism. It is not infrequent to see a person who has been a pretty confirmed alcoholic begin to almost spontaneously and without signing any pledge, taper off when he gets in his late fifties and sixties. Apparently if they survive this long, they lose their addiction or appetite or something. But it is not unusual at all to see these older alcoholics just quit drinking. This is no change of heart, no conversion, or anything, they just quit drinking.

But I would also point out that it is not unusual to find that among——

Mr. Fogarty. What is the easiest way to quit?

Dr. Felix. Well, I do not mean to be flip, but I can tell you, it is to quit.

Mr. Fogarty. The only reason I ask this, I heard Dr. Terry asked at the Press Club Tuesday what was his recommendation on how to quit smoking. It was a serious question.

His answer was, well, the best advice he could give would be to get up in the morning and say he was not going to smoke a cigarette that day. Then try it the next day and see if he could keep on this way, but not to say to yourself, "I am never going to smoke another cigarette."

Dr. Felix. That is right.

What I tell my patients as far as alcohol is concerned is, "Look, just do not take that first one, do not drink today, then tomorrow we will worry about that. But do not drink today and do not drink tomorrow until you check with me," which means when you check with me I say wait today, too, No. 1.

No. 2, always remember this, if you are an alcoholic, you are a helpless alcoholic unless you stay dry. You will be an alcoholic until your dying day. If you are dry for 20 years, you are still an alcoholic. You never get over being an alcoholic. You cannot ever drink again.

These are hard facts.

Mr. Fogarty. That is pretty rough treatment.

Dr. Felix. Yes, it is.

DEFINITION OF ALCOHOLIC

Mr. Fogarty. What is your definition of alcoholics?

Dr. Felix. An alcoholic is a person who consumes alcohol to the point of intoxication, so that it is beyond his power to control his drinking. He has lost his power of self-control with regard to the addiction.

Mr. Fogarty. Where it starts to interfere with his work——

Dr. Felix. Interfere with his work. There are some other criteria we use. Roughly, it is the person who tends to drink alone; the person who, when he goes out to fix drinks for the group, always takes two quick ones before his wife catches him at it; and the fellow who needs one in the morning pretty regularly to open his eyes.

There is an interesting phenomenon we notice in these alcoholics. When a person finally reaches a point where he loses control and he starts drinking uncontrollably, very frequently something happens just before that. And this is one of the real final warnings. The fellow frequently will suddenly develop what we call a hollow leg. All of a sudden it seems as though he can drink any amount and not turn a hair. This might last from 6 months to a year and then he finds he cannot stop.

We do not know why this is, and I can only speculate, and this would not be fair except to give you some insight. It may be that this is the last stage before the body becomes so addicted to the drug that he cannot let it alone, when his resistance to it is at its highest so he metabolizes it much more rapidly than the average person does.

Incidentally, you mentioned quitting or not quitting. As you know, I smoked cigarettes for 45 years without ever trying to stop. And 2 years ago, I can tell you the day and the hour; that is why I know I am still a tobacco addict—at noon on the 12th of March, 2 years ago, I decided to stop for a few days because of the season of the year. I had gone 3 or 4 days, and I was on a radio show down here, and the lady who was conducting the interview would not tell me what she was going to ask me. There had been a few newspaper articles, as happens now and then, and I did not know what was going to happen, and I was getting more and more nervous. At the halfway break for the commercial, she tossed a pack of cigarettes out and said, "Have one." Before I thought what I did, I pulled one out and lit it. I was shaky, like this. The first thing that tipped me off like this was, when I took a deep drag and inhaled, I got dizzy. I had gone 4 or 5 days without a smoke. I could not figure what had happened. Then I remembered. I was so disgusted with myself that I could not control my own habits for as long as that, I ground that cigarette out and said, 'It will be a cold day in July when I smoke again." I have not smoked since then. I do not intend to ever smoke again. All I can do is say, "I will not smoke today." I was smoking two packs a day.

Mr. Denton. How much weight did you gain?

Dr. Felix. Eighteen pounds.

Mr. Denton. I gained 20.

Dr. Felix. I would like to add one thing for the record. It is one of our great achievements this year. I have a copy I can leave with the committee, if Mr. Moyer would like to have it here in the file. "Alcohol and Traffic Safety" is a book published by the Institute this year as a result of a conference held in Pittsburgh by highway police and psychiatrists, and others, on some of the problems in the field of traffic safety as it relates to alcohol and drinking and drinkers. I think it is a landmark piece of work.

This was done cooperatively with the Bureau of States Services, Division of Accident Prevention. So it is a Public Health Service activity jointly sponsored by the National Institutes of Health and the Bureau of State Services.

Mr. Fogarty. We will also place your special report in the record.

(The report referred to follows:)

Special Report: Alcoholism

The National Institute of Mental Health program in the field of alcoholism is providing a base for expanding activity as well as meeting various immediate needs. These needs are to increase research and demonstration projects, consultation, technical assistance and training programs, attraction of competent professional personnel to the field, and assessment of the current state of knowledge about alcoholism.

Given rise to alcoholism is a complex interplay of physical, psychological, social, and other factors. The extent to which each of these factors contribute to the alcoholism syndrome is unknown. Progress is being made toward its understanding. However, there is a need for more knowledge about the specific causes of alcoholism to aid in reducing its incidence and prevalence and for evaluative studies of various therapeutic approaches and procedures.

Increased attention is being given to the use of available knowledge, facilities and professional skills, and to the role of interested citizens in developing more comprehensive programs. These would include planning leadership; education; consultation; case finding, case holding, and referral; treatment; rehabilitation and aftercare, as well as research and evaluation.

PROGRAM DEVELOPMENT

Four projects pertinent to the institute's program were initiated a few years ago. Their basic purposes are to clarify and assess existing knowledge, and to provide a broad understanding of drinking behavior so that more effective prevention and intervention methods can be provided. Currently, emphasis is being placed on consolidating much of the work which is underway.

Nomenclature.—This project is planned to bring some order to the present confusing sttae of terminology used in the alcoholism field. How various terms are being used, and their generic meanings, are being studied to establish a nomenclature suitable for research and clinical purposes.

Influence of sociocultural factors.—This research conducted at the University of Colorado is concerned with behavior, including alcoholism, in a triethnic population. The 5-year project is in the final phase of data analysis to determine the relationships between factors associated with deviant behavior, on the one hand, and drinking on the other. Preliminary findings have been reported at several national professional meetings. For example, the amount of drinking and the amount of deviancy associated with it are greatest in the American Indian group, intermediate in the Spanish-American, and least among the Anglo-American. Rates of drinking and deviancy are also correlated with both group and individual attitudes, such as, acceptance of social norms, expectations for the future, close parent-child relationships, and available models for deviant behavior. Analyses in progress will determine how much of the drinking in each group can be attributed to each of the social, psychological and cultural factors studied, and how they function in combination to increase or decrease the likelihood of excessive drinking.

Cooperative Commission on the Study of Alcoholism.—The commission, incorporated in California, was formed about 3 years ago as a result of efforts by institute staff members and the North American Association of Alcoholism Programs, an organization of State and local alcoholism program administrators. The commission is made up of 20 members representing relevant scientific disciplines.

Major tasks of the commission are: (1) To make a comprehensive study of scientific knowledge now relating to alcohol use and alcoholism; (2) to inventory, study, and evaluate activities, programs, and resources playing a significant part in attempts to solve or control the problem of alcoholism; (3) to investigate relationships between alcoholism organizations and other resources such as those in the fields of mental health, tuberculosis control, correction, and professional schools for the training of treatment and research personnel; (4) to use the results of these studies to formulate policies and recommendations for improving treatment, education, and prevention; and (5) to identify in broad terms what further research is needed.

The cooperative commission, through its staff at the Institute for the Study of Human Problems at Stanford University, has initiated or stimulated investigations in a variety of fields through conferences, projects, and studies. These include conferences on anthropological and psychological theory and research as related to drinking and alcoholism; and on biological aspects of drinking and alcoholism; projects such as one in San Francisco concerning the dynamics of various groups mobilized in a joint attack upon alcoholism; and the study of the total "alcoholism apparatus," which is examining ways in which existing resources are being used to deal with alcoholism and other alcohol-related programs; and assessing strengths and weaknesses of these programs during the past 20 years with a view to making various recommendations.

Such studies indicate the attempted synthesis being made in the vast field encompassed by the term "alcoholism problems." At the same time, no attempt is being made to dictate the operation of programs and services, or to undertake all of the scientific and social investigations needed. As pathfinder, stimulator, inventory taker and perhaps, prognosticator, the cooperative commission should make possible the entry of new forces, new agencies, and new ideas into the area, while assisting programs and established investigators.

Alcohol usage patterns.—This project is divided into two phases, the first of which—instrument development—has been completed and field tested. The results of this pilot study of 1,268 persons from a random geographical sample in San Francisco indicate that both sampling methods and questionnaires are satisfactory and showed interesting, and perhaps unexpected findings as to which subgroups of the sample are heavy drinkers. However, projection of the drinking patterns of various groups in the sample to the universe population may have to await enrichment of the sample before generalizations can be made.

The second phase—a national study of the nonpathological use of alcohol, from which consumption baselines are to be developed—is currently in progress, or will be initiated, in various locations. In San Francisco the second series of interviews has begun on the same study population, and interviewing will be initiated in two selected cities, in the early part of 1964. Repeated interviews of these and various other population samples will, it is hoped, indicate shifts in consumption, perhaps indicating when, by whom, and under what circumstances, deviant drinking patterns are formed.

TRAINING

Training pertinent to alcoholism is an integral part of the general training program in psychiatry, psychology, social work, and nursing.

Two training grants pertain specifically to alcoholism. One is planned to acquaint casework students with treatment and rehabilitation programs for alcoholics, as well as to provide skills in community organization essential to State and local program development, public education and volunteer activities. The other grant is designed as a pilot project to prepare predoctoral social science students through research and seminar activities for work in alcoholism.

Because the medical profession has a key role to stimulate community interest and understanding of the alcoholism problem and to provide services in their offices and in general hospitals, the grants for training of general practitioners and residents are very important.

Plans are well underway to assist State mental health authorities and others in a program of inservice training. Activities will include preparation of resource material, development of pilot projects, and provision for regional conferences in which various problems, including that of alcoholism, will get attention.

A number of 1-week schools or institutes of alcohol studies associated with a college or university have been provided consultation and resource personnel. A mental health project grant assisted the 4-week Summer School of Alcohol Studies at Rutgers University, New Brunswick, N.J., in evaluating and revising its activities.

RESEARCH

Because no one factor has been found so far to produce alcoholism, studies are being supported in many areas of research, ranging from basic biochemical studies to studies on complex social relationships. For example, they include metabolism of ethyl alcohol, the effects of ethanol on neurohumoral amines, induced alcohol addiction in animals and ethanol metabolism in prolonged ingestion of alcohol. Among the studies in sociocultural areas are studies of normative controls and the social use of alcohol, and of the prevalence of alcohol in an urban community.

Support is provided also for assessing the effectiveness of various forms of treatment. Such studies relate, for example, to personality changes in therapy of alcoholics, to drug therapy for depressed and schizoid alcoholics, and to preventive casework with the families of alcoholics.

Some studies in the basic disciplines—physiology, biochemistry, psychology, and sociology—are indirectly related to alcoholism and may contribute to its control. The Center of Alcohol Studies at Rutgers University in New Jersey has an institute research grant for various investigations. A health research facilities grant from the Public Health Service is helping to provide a new building to house the center.

An increasing number of mental health project grant applications are being received. Active projects include demonstrations, pilot studies, conferences and administrative research. Currently, 16 mental health projects are categorized in the area of alcoholism, while 7 more in another area have alcoholism aspects.

An early mental health project grant was made in 1959 to Massachusetts General Hospital in Boston, to study "Alcoholism Treatment and Initial Therapeutic Contact." Work centered in its emergency ward, and findings show that alcoholics receiving initial care and attention from well-prepared personnel enter and continue treatment far more often than similar patients not getting such consideration. Under a recent grant, a rural hospital research and therapy unit for alcoholism, with Massachusetts General Hospital personnel as consultants, is studying how approaches used successfully in a large city might be applied in a small one.

PROFESSIONAL AND TECHNICAL ASSISTANCE

Central and regional office personnel provided increased technical assistance and consultation about alcoholism during the year. Much of this pertained to mental health project grants. However, the initiation of work relative to planning grants, to inservice training, and to hospital improvement grants contributed to the demand for such services.

Eleven technical assistance projects (TAP's) pertinent to alcoholism received support and were cosponsored by the Institute in association with State agencies. They were: "Interagency Development and Coordination of Services for Alcoholics and Their Families" (Alabama), "Program Planning for Control of Alcoholism in a Metropolitan Community" (Los Angeles), "Clergy's Role in the Problem of Alcoholism" (Louisiana), "Alcohol Education" (Michigan), "Planning for Coordinated Alcoholism Services on a State and Local Level" (New Hampshire), "Problems of Alcohol as Related to Youth" (North Carolina), "The Alcoholic and the Court" (Oregon), "Mobilizing Public Agencies in the Rehabilitation of the Alcoholic" (Rhode Island). One held in Pennsylvania on "Key Issues in Prevention of Alcoholism" gave attention to epidemiology and had participants from the 10 States of regions I and II. "Alcohol Education in Institutions of Higher Learning" (Mississippi—for the 6 States of region IV) and "Interpreting Current Knowledge About Alcohol and Alcoholism for a College Community" (New York) were the first technical assistance projects giving attention to higher education. Published reports on each project receive selective distribution. The projects have contributed to program development, and some have stimulated preparation of mental health project grant applications for demonstrations or studies.

A 4-year demonstration project, which the Institute carried on in collaboration with the Prince Georges County, Md., Health Department, ended in June 1963. This program, initiated as a public health approach to the problem of alcoholism, is being continued with county funds. Judging by early results, it appears essential, in providing rehabilitative services for the alcoholic and his family, to plan for continuity of care, both in terms of working relationships between staffs of outpatient and inpatient services and between those providing clinical services and those rendering other community services to the alcoholic and his family. A final report on the demonstration is being prepared.

STATE DEVELOPMENTS

Alcoholism program development in West Virginia was aided by its 1963 legislative session which made an additional $25,000 available to the State department of mental health (State mental health authority), with the requirement that a division of alcoholism be established. The Division of Mental Hygiene, Wisconsin Department of Public Welfare (State mental health authority) received State funds for additional staff positions to initiate study and planning relative to alcoholism. In April 1963, the Governor of Maryland charged the State board of health and mental hygiene with responsibility for functions of the Maryland Commission on Alcoholism. In May 1963, the board assigned the responsibility to the State Department of Mental Hygiene. Nevada legislation established a State department of health and welfare which includes an alcoholism division having the functions of the former State alcoholism agency.

There are 10 State commissions, boards on alcoholism, or other separate agencies for alcoholism. Their staffs have a working relationship with those in public health, mental health, education, welfare, and others. Of the other 44 States and territories, limited attention is given to alcoholism in 6 or 7. Most of the States give specific consideration to alcoholism in the State department of health (some of which are the State mental health authorities) or in a State mental health authority (other than a State health department), such as the Connecticut, Illinois, Indiana, New York, and Tennessee Departments of Mental Health or Mental Hygiene, Louisiana Department of Hospitals, and others.

The mental health planning underway in all States and territories has stimulated increased attention to alcoholism. Approximately 20 States have a "task force" on alcoholism, while several others are approaching the problem in other ways.

Many State hospitals have or are developing "units" for patients having alcoholism diagnoses. It is expected that some of the hospitals will seek a hospital improvement grant to organize a special program for alcoholics as a way to improve the total hospital treatment program. The development of in-service training programs in such hospitals will have impact also on the treatment and rehabilitation of alcoholic patients.

Alcoholism program development will receive further stimulation in the planning and development of community mental health centers. State and local, public and voluntary, health agencies are showing increased interest in alcoholism. For example, a report on "State Department of Health Responsibilities Relating to Alcoholism" was prepared by the Institute for use at the 1963 Surgeon General's conference with the State and territorial health officers. A recent mental health project grant to the American Public Health Association for a 3-year period is designed to aid in developing "A Guide to Public Health Control of Alcoholism."

At this time, the Bureau of State Services is considering the public health activities which it can carry on in coordination with the Institute, complementary or supplementary to activities now underway. Work in accident prevention activities is an example of coordinated effort between the Bureau and the Institute.

The Secretary of Health, Education, and Welfare arranged a national conference on alcoholism, held July 9 to review the Department's activities and plans in this area. The Institute assisted in preparing for the conference and in preparation of its final report.

DREAMS

Mr. FOGARTY. You mentioned in your justifications that you are doing some research on the subject of dreaming. What are you doing in this area?

Dr. FELIX. Oh, yes. These are studies carried on primarily in the intramural programs as well as through research grants. That is, our own staff are doing studies on this, but there are also a number of studies done elsewhere.

These studies are attempts to try to understand dreaming and what its role is as far as normal healthy life is concerned, and in mental illness.

You may remember that we found that people, all people, dream and that the dreams may occur in bursts, or may stretch out over a longer period of time, but they occupy a significant part of a sleeping period.

Dreaming has been—do not ask me how because this is a technical thing and I did not prepare myself for it, so I am just recalling what I know—the fact that an individual is dreaming can be determined by some measures that have to do with the depth and rate of respirations and how they change, and the way the eyes move when asleep, brain wave patterns, and so forth.

They have found when they interrupt dreaming, whenever a person gets to the dreaming stage and they interrupt it, that the person tends to become anxious and depressed—even though he gets enough sleep; that is, you can interrupt the dreaming without waking the person, just raise the depth of the sleep a little and the person becomes emotionally quite tense on awakening. Also, as you know, by inducing sleep a person who is tense or tends to be mentally ill, sometimes improves. Investigators now want to determine what role dreaming plays in the improvement.

Again, these are empirical findings. These are things they have found go together. Why, we do not know, but we think it is worth tracing down. It is an interesting thing that since the days of early man, everyone has attached some connection to dreaming and the mental state. It has been all sorts of things. Nebuchadnezar had a dream. Daniel had to interpret it for him. And through the years Saul had dreams, and so forth.

Again, as Dr. Shannon said this morning—I believe it was this morning—about some of these psychoactive drugs, they were used by folk doctors in India. I have come to feel as I have gotten older that there is nothing we can shrug off as far as folklore is concerned until we know what can be shrugged off. Here we are again back to something like this.

Mr. **Fogarty**. Someone might ridicule something like this and I thought we should have an explanation in the record.

Dr. **Felix**. This is very serious research with exciting results.

CHILD RESEARCH

Mr. **Fogarty**. How are you making out on the project, personality development of children?

Dr. **Felix**. Do you want me to give it to you here or put it in the record?

Mr. **Fogarty**. Tell us about it.

Dr. **Felix**. This is a very interesting project which has been carried on for some time, Mr. Chairman. I will make a brief statement about it if it is agreeable to you.

Mr. **Fogarty**. All right.

Dr. **Felix**. It has been known for many years, from time immemorial, I suppose, there has been a discussion over what is the role that inheritance, or what one brings into the world with him in terms of his personality, and what is the role of the environment in which a person finds himself.

It has been particularly difficult to separate these. As it should be, children are born into homes and come under the care of their mother and/or father very quickly. In the old days they came under the care of the mother immediately, when they were delivered, as my father used to deliver them in the farm homes out in the plains of Kansas.

We have found a way to make studies at significant points in the child's life which allow us to separate what we think is due to nature, separate that from nurture. Briefly, it is this: Young married people living in Montgomery County, Md.—we have used people only from this area who were going to be there as far as we can tell for some time and who, after having had the project thoroughly explained to them, have volunteered—are interviewed in the third month of their marriage. They are given a series of psychological tests and personality tests to get some idea in the case of each of them what their personality is like, how they look at marriage from the point of view of adjusting to a marriage partner, how they look on children, and what their attitude is toward having children, raising children, being a parent.

They are then followed, kept in touch with, so that we know something about them and know where they are. And in the seventh month of the lady's first pregnancy, she is brought in for a number of hours of retesting, reevaluation, to see if now that this event is about to come to pass, she looks at parenthood and children and home as she did during the fourth month of her marriage, which may have been some time ago. The father is also checked.

After the birth of the baby, the child is given a very exhaustive battery of tests between the second and fourth day of its life to get some baseline information as to what the child's fundamental personality is like. In other words, can we find out what the child brings with him into the world before it has much contact with its father, mother, or anyone; what kind of reactions does it have?

I might parenthetically mention here that you have heard me describe in the past something that we think at this point is an inborn tendency of people, children, what we call the cuddly and the noncuddly child. I admit that it is a poorly chosen word for that purpose, but what it amounts to is this: Some children enjoy being handled and fondled. The mother can bathe and make over and tickle and cuddle and they love it. Other children just plain do not like it and after a little of this, they will get fussy, tighten up, bring elbows down and knees up and get red and start to cry.

This apparently is an inborn trait. We began to suspect this, and what we wondered was what happens if a mother who doesn't like cuddling gives birth to a cuddly baby? How does the baby react to this? Is this a real need of some children more than others? Or what happens, even more so, if a mother who likes to cuddle gives birth to a noncuddly baby and she wants to love and fondle it and after a little bit the baby starts saying in its own little way, "Go away." What happens? How does the mother feel? Does she feel the child is rejecting her? What happens?

Suppose that the father is not of the same category as the mother, and so the child tends to orient toward one more than the other, depending on which one is like him or her? And what does this do and how can we help by being able to determine these things and counseling the parents?

Well, then, at 3 months of age, the child and the mother are brought in for about 8 hours, usually from about 1 o'clock in the afternoon until about 9 o'clock at night. In this present temporary building we have now which will have to be torn down—and the reason this all came about was because we were advertising for bids to rent a new building. It has to be torn down to make way for the new cancer research building and new mental health-neurology research building.

There are kitchenettes in there, a little bathinet for the baby, and a dining room, so that we can observe over a number of hours how the mother cares for the baby, how the baby responds to the mother, the mother responds to the baby, how they both respond to the father coming home, and what the routine is during the meal, feeding of the baby, and so forth.

Now, this is observed through a one-way window. The parents are well aware of the fact that they are under observation in these areas at these times. They are always told when they are to be observed.

Now, where we apparently got into trouble on this project: to be crystal clear that this was exactly what was to be studied and nothing else, we went one step further and said in our specifications that no other areas would be observed. And I think the word "bedroom" was mentioned. Just because someone might get dirty-minded and think the wrong thing, we wanted to be very clear. As we all know, evil, like beauty, is in the mind of the beholder. Somebody saw the summarized version of the advertisement for bids and for his own reasons turned it around and apparently thought this is what we were looking at. There are no bedroom scenes in this. There are no bedrooms in this. This is strictly the other end of the house, kitchen, dining room, and so forth.

After this particular session of about 8 hours, the child then goes back. We keep in touch with the family, and at about 30 months of age, the child is brought in for 1 month, 2 hours a day, 5 days a week to a nursery school we maintain for this purpose. The child is brought into contact with other children, and these are all children on whom we have complete data. We have made predictions—this is part of the procedure—as to how this child will react with other children of various kinds, and we know the makeup of each of these children.

These children are watched during these 2 hours, when they get their juice and their nap and play with each other in this little play yard. The play yard is a simulated outdoor yard. Somebody made a crack about this, and I can only say we have to schedule these because we have a number of people in the study, and if it is a rainy day we cannot take little children outside. If you have a simulated yard inside that looks a bit like outside, you can operate in all weather. The children are observed during this 2-hour period by skilled observers who take notes on each child's behavior and interaction with other children.

This study will go on, and there will be another period of study later in the child's life. We have not gotten beyond this stage yet because none of the children are older than this. We will follow these children through 5 years of life. And on the basis of this, after we have a large enough series, it is our hope that we will be able to make some definitive statements about the role of inheritance as contrasted to the role of environment on the development of personality of children.

Now, some of the reasons why this is important. What about children who are reared in orphanages? And some children, unfortunately—just one of those tragedies of life—this is what their fate is. What advice can we give to people who run homes for parentless, motherless, fatherless children which will make it possible for these youngsters to have a richer, fuller life and better promise of a good future as adults? What can we tell the foster parents—and there are a lot of these—who adopt children? How can we advise them best to deal with this child—how can we examine the child and examine the parents or the foster parents so that there can be the best possible concordance of effort for the best outlook of the child? There are other reasons, too.

These have very practical, very real, and, I think, as a physician, very poignant purposes, which are, I think, undeserving of the ridicule and criticism they have received by the press and some people.

THERAPEUTIC DRUGS

Mr. Fogarty. Now, would you like to add anything to what you said in your opening statement on therapeutic drugs?

Dr. Felix. I have a briefing document here which I would be very glad to supply to amplify what I have to say if you wish.

Mr. Fogarty. All right.

(The material referred to follows:)

Special Report, Psychopharmacology Service Center, Clinical Neuropharmacology Research Center

INTRODUCTION

During the past year the Psychopharmacology Service Center program of collaborative clinical studies for the evaluation of drug efficacy in psychiatric patients has been progressing well. Activities under the special grant program in early clinical drug evaluation have also been progressing effectively, and grant-supported clinical research activities have begun in some important new areas. Methodological developments growing out of both special and regular grant-supported work in clinical psychopharmacology will be of significant value to future research in this area. Work at the preclinical level dealing with effects of psychoactive drugs on animal behavior, brain function, and brain biochemistry, as well as work on the metabolism of these agents, is proceeding satisfactorily, although basic research in these areas must clearly be viewed as a long-term investment—of great importance to psychopharmacology in particular and to mental health and behavioral science in general.

CLINICAL RESEARCH

Acute schizophrenia

The initial NIMH–PSC collaborative study in this area shows clearly that the three phenothiazine drugs used—chlorpromazine, fluphenazine, and thioridazine—do not differ significantly from one another in their effect on any of the major symptom areas characteristic of the acute schizophrenic patient. The major contribution of the drugs lies in areas generally thought to be more characteristic of serious schizophrenic illness and not generally regarded as responsive to phenothiazine treatment. These areas include the patient's indifference to his environment, slowed speech and movements, other behavioral symptoms such as giggling and grimacing, and poor self-care. It seems clear that the drugs do more than simply tranquilize excited patients; they have a broader effect which could be characterized as antischizophrenic or antipsychotic.

An analysis of changes occurring in patients who did not manifest any psychopathology in a variety of symptom areas on admission to the hospital was undertaken to determine whether the phenothiazines might be producing some symptoms—such as slow speech and movement or indifference to the environment—at the same time that they were alleviating other symptoms. The analysis reveals the opposite to be true: patients on placebo developed symptoms in a number of areas, where they had shown none on admission, to a significantly greater extent than patients on phenothiazine treatment. It must be concluded that the phenothiazines do not only cause a reduction in symptoms present on admission but also prevented the appearance of new symptoms during hospitalization.

The second NIMH–PSC collaborative study of drug efficacy in acutely ill, newly hospitalized schizophrenic patients (involving eight of the nine original hospitals) is now well underway, approximately half the necessary number of patients having been admitted to the study. The efficacies of two of the original drugs, chlorpromazine and fluphenazine, are being compared with that of a newer phenothiazine, acetophenazine, to determine whether or not the new drug's specificity for paranoid schizophrenia, evident in a smaller early clinical drug evaluation study, can be confirmed. This study will also extend the period of controlled drug treatment to 26 weeks to determine whether or not the substantial improvement noted at the end of 6 weeks in the first study will continue for as long as 6 months. Further, since the subjects in the second study will be followed as outpatients on controlled drug treatment, possible differences in the safety and usefulness of the three phenothiazines as maintenance treatment in patients returned to the community can be observed. Again, the results of certain specialized statistical approaches being utilized in examining the data from the first study—as discussed in more detail later—can be checked against the data from the study now in progress.

Since no new drug of outstanding promise for the treatment of acute schizophrenic reaction has appeared in the past 2 years, further studies to compare drug treatments in newly hospitalized schizophrenic patients do not appear to be warranted at the present time. Instead, a cooperative study of drugs in chronic schizophrenia, and another of drugs in depression are being developed to begin late in 1964 as the collection of data from the second study of acute schizophrenia is completed.

Depression

Two major controlled studies of treatment efficacy in depression are in essence completed. One of these, in the New Jersey State hospital system, has compared iproniazid with electroconvulsive therapy and placebo, and subsequently has compared imipramine with electroconvulsive therapy and placebo. Both studies were carried out in premenopausal female depressed patients admitted to several New Jersey State hospitals. A similar study was simultaneously carried out in three Massachusetts State hospitals, coordinated by a group at the Massachusetts Mental Health Center. This study has been comparing electroconvulsive therapy, imipramine, phenelzine, isocarboxazid, and placebo in all depressed patients admitted to these hospitals, including schizophrenic patients manifesting major depressive symptomatology.

The results of these two independent studies are contradictory and pose serious problems. The Massachusetts investigators have reported that electroconvulsive therapy clearly is the best single treatment of depression. One of the two monoamine oxidase inhibitors studied, isocarboxazid, has also been shown to be clearly inferior to placebo in the treatment of these patients. A similar finding has emerged from a collaborative study of drugs in depression carried out by the Veterans' Administration. The Massachusetts study has not been able to show imipramine or phenelzine to be significantly superior to placebo. The data show a trend in favor of imipramine in severe psychotic depressive reactions. The results in neurotic depressive reactions, however, fail to show even a trend in favor of this drug. These findings are in direct contrast to those of the New Jersey study, which involved almost exclusively neurotic depressions. Here imipramine was as good as electroconvulsive therapy, and both these treatments were clearly superior to placebo. These conflicting results parallel those in the clinical literature on controlled studies of imipramine. Although some studies show that imipramine is definitely superior to placebo, several fail to do so.

A controlled outpatient study comparing imipramine with placebo in neurotic depressive reactions has recently been completed at the Johns Hopkins Hospital. This study, using a 4-week control treatment period, was able to pick up a superiority of imipramine over placebo only at the end of the first 2 weeks;

by the fourth week, this difference had disappeared. The reasons for the conflicting results of controlled studies are unclear. Clinicians in this country generally agree that imipramine is a good drug, efficacious in the treatment of depression.

A grant-supported study at Hillside Hospital (Glen Oaks, N.Y.) has shown that both imipramine and chlorpromazine are superior to placebo in the treatment of depressed patients. Chlorpromazine's superiority, the results suggest, may be greatest in depressed patients showing agitation or paranoid ideas; imipramine seems more effective in depressives lacking these features.

Anxious neurotic patients

An NIMH–PSC collaborative group involving three outpatient departments has now completed two studies. The first showed meprobamate to be superior to placebo in the treatment of anxious neurotic patients. The study suggested that either the physicians' enthusiasm or his suggestion to the patient, that drug side effects are related to drug benefit, might have increased the drug's apparent effectiveness. The second study has compared chlordiazepoxide with placebo. Half the placebo and half the drug patients also received a small amount of atropine sufficient to produce the side effect of dry mouth, which had been purposely suggested by the physicians as being a sign of effective therapy. Analysis of the data from this study indicates that chlordiazepoxide is significantly superior to placebo. The addition of atropine, with or without the suggestion that dry mouth would be a positive sign of improvement, has proved to have no effect on observed symptom change in these patients.

A British grant-supported collaborative study involving a number of general practitioners has compared chlordiazepoxide with amobarbital, a barbiturate widely used in Britain for the control of anxiety symptoms. The results of this study failed to show any superiority of the newer drug over the standard barbiturate. The dose of chlordiazepoxide used in this study was, on the average, somewhat lower than that used in the NIMH–PSC collaborative study.

A grant-supported study at the Downstate Medical Center in Brooklyn finds that both chlordiazepoxide and chlorpromazine are superior to placebo in the treatment of anxious neurotic outpatients, while meprobamate, used in half the dosage used in the first NIMH–PSC study, was not superior to placebo. A University of Pennsylvania study has shown meprobamate to be superior to placebo and superior also to a low dose of phenobarbital.

NIMH grantees at Hillside Hospital have reported that imipramine, generally regarded as a treatment for depression, has a dramatic and specific effect in relieving severe chronic phobic, anxiety symptoms in patients who have failed to respond to a variety of tranquilizers, psychotherapy, and, sometimes, electroconvulsive therapy. This is of special interest because these patients were clearly not depressed, and yet responded so well to the drug.

Other clinical studies

A grant-supported study at Spring Grove State Hospital finds that chlorpromazine, triflupromazine, prochlorperazine, perphenazine, thiopropazate, trifluoperazine, fluphenazine, and thioridazine, are highly similar in their effects on newly admitted psychiatric patients requiring phenothiazine treatment.

A study carried out at the University of Minnesota was unable to identify significant differences between thioproperazine and chlorpromazine in chronic schizophrenic patients.

Further analyses of a phenothiazine study in chronic schizophrenics carried out at the Napa State Hospital in California indicate that chronic patients with a pyknic; that is, a square or large-boned body structure show a much higher likelihood of significant improvement and release than schizophrenics having other types of body structure.

A grant-supported study at the VA Hospital in Bedford, Mass., has reconfirmed the fact that intravenous injections of amobarbital, in this case combined with a stimulant, methamphetamine, can produce a temporary burst of speech and communicativeness in otherwise completely mute, chronic schizophrenic patients. This startling psychopharmacological effect, though well known and frequently studied in the late 1940's, has received very little attention in recent years.

A study being carried out under special grant support at New York University has shown that chlorpromazine is superior to placebo in the treatment of behavior disorders in disturbed children between the ages of 6 and 12. In particular, the drug was effective in patients showing schizophreniclike autism and in those manifesting less extensive disorganization but showing anxiety, instability, short attention span, and a generally poor adjustment to their environment. These effects were not evident in children with neurotic anxiety nor were they apparent in children with aggressive sociopathic tendencies. The study underlines the fact that classification of patients into major types greatly clarifies the contribution of drugs to improvement. Patients in the last two groups did quite well in the hospital environment, whether on drug or placebo.

A study carried out—under a grant at Johns Hopkins Hospital—both in a training school setting and in a special home for dependent children not suitable for ordinary foster home placement, finds that methylphenidate not only caused behavioral improvement in anxious disturbed children but also resulted in better performance on psychological tests measuring learning ability. This work extends an earlier study that demonstrated the same general effects for dextroamphetamine. In both studies, subjects receiving the drug treatment showed little or nothing in the way of adverse subjective effects; however, there was some suppression of appetite and loss of weight.

Work on drug efficacy in childhood schizophrenia is covered in the "Special Report on Schizophrenia."

The early clinical drug evaluation program

This program now encompasses 17 units actively engaged in the study of the newer psychiatric drugs. The work ranges from very early studies of very new drugs to small controlled comparisons with better known drugs. Included in the 197 drugs that have been studies are 42 phenothiazines, drugs related to chlorpromazine; 14 drugs related to chlordiazepoxide; 6 butyrophenones, drugs related to halperidol (which is widely used in Europe to control the acute schizophrenic and manic states, but which has received little acceptance in this country); benzquinamide, a tranquilizer structurally related to reserpine; 11 monoamine oxidase inhibitors related to iproniazid and phenelzine; 14 drugs relate to imipramine; and a variety of miscellaneous drugs studied because of their sedative or stimulant effects in animals or because of their biochemical properties.

Benzquinamide, one of the drugs on the list, has been reported by a small, grant-supported collaborative study group composed of several Veterans' Administration hospitals, to have an efficacy in newly admitted schizophrenic patients comparable to that observed with potent phenothiazines. The drug was observed, however, to show greater variability in response, with some patients getting much worse than was usually observed with phenothiazines, and others doing quite well. A controlled study of this drug carried out in another early clinical drug evaluation unit in Louisiana reported significant worsening on benzquinamide vis-a-vis both chlorpromazine and placebo in chronically hospitalized schizophrenics. These adverse effects included both exacerbation of psychotic symptoms and increased depression and intensification of selfdestructive behavior.

A grant-supported study of a newer phenothiazine, thioproperazine, conducted at the Verdun Protestant Hospital, shows the drug to be a potent tranquilizer comparable to other phenothiazines in chronic schizophrenic patients. There is some suggestion it may be particularly effective in the treatment of manic excitement. A study at the same hospital of desmethylimipramine, a new antidepressant that is also a normal metabolic product of imipramine, finds the drug to be an effective antidepressant and one that tends to be a little faster acting than imipramine. In rats, the new drug is clearly more potent and faster acting than imipramine; in depressed human beings, the difference appears to be considerably less.

The most promising compound to emerge from the early clinical drug evaluation program during the past year is triperidol, a butyrophenone chemically related to halperidol, but more potent and somewhat more stimulating in its activity while possessing major antipsychotic properties. This compound has been reported by a grant-supported early clinical drug evaluation unit in Paris to have special efficacy in the treatment of underactive retarded chronic schizophrenic patients. This finding was confirmed in a controlled doubleblind study carried out by an early clinical drug evaluation unit in Louisiana. Compared with chlorpromazine in a group of chronic, severely treatment-resistant schizophrenic patients, triperidol was found by the Louisiana unit to be significantly superior. A related compound, haloanisone, studied by an early clinical drug evaluation unit in New Jersey, appears to have some promise in the treatment of chronic schizophrenic patients. Several grant-supported investigators who have had experience with these compounds are unanimous in feeling that the butyrophenones produce improvement in chronic patients more rapidly than the phenothiazines. These compounds deserve, and will receive, futher study.

Two grantees have reported on studies of the efficacy of phenothiazines in combination with an antidepressant drug. An investigator at the University of Minnesota compared trifluoperazine alone with trifluoperazine plus tranylcypromine in patients diagnosed as schizophrenic who also showed evidence of depression. Only a very slight and statistically nonsignificant trend in favor of the combined drug treatment is reported. Another investigator, at Stanford University, has reported on a small collaborative study in several Veterans' Administration hospitals, that evaluated a combination of perphenazine and amitriptyline, a drug related to imipramine, in newly admitted schizophrenic patients. The results of this treatment, compared retrospectively with a previous study of perphenazine alone, reveal no significant therapeutic advantage attributable to the combination. However, there appears to have been some tendency toward a reduction in neurological side effects, a reduction attributed by the investigator to the anticholinergic and, presumably, anti-Parkinsonian effect of amytriptyline. Combined treatment of this sort is widely used, but to date there is no firm evidence that it offers any superiority over phenothiazine treatment alone in the therapy of schizophrenic reaction.

The Early Clinical Drug Evaluation Unit investigators are brought together twice a year to discuss common problems and new drugs studied. The most recent meeting held in the fall of 1963 included a symposium on drug toxicity with presentations by nationally known experts on drug-induced liver toxicity, toxic drug effects in the blood, and drug effects on the skin. The generally accepted norms for various liver function tests, it was reported, are probably incorrect. The extent and range of normal variability on these measures, either in normals or in patients receiving placebo treatment, are considerably greater than usually assumed. Further, the variability and relative unreliability familiar to research psychiatrists in the use of rating scales were reported to be found also in laboratory determinations. Rather than stopping the drug after a single abnormal finding, a second laboratory test should be run immediately to determine whether real pathology exists or whether laboratory variability has resulted in an apparently alarming finding that disappears on repetition. Within our group of grant-supported investigators, it became evident at the meeting, there exists an unusual wealth of data on changes in blood counts and liver function in psychiatric patients receiving placebo.

Psychotomimetic agents

The past year has shown an increasing popular and medical interest in the psychotomimetic agents (compounds producing psychoticlike symptoms), such as LSD[25] (lysergic acid diethylamide), psilocybin, and mescaline. This is probably caused by increased concern over the potentially serious side effects of these agents when taken without intensive and skilled medical supervision. There appears to be an increasing illicit traffic in these agents, which are, apparently, being self-administered in major urban centers for "kicks." Acute sequelae of such self-administration, including suicidal attempts and prolonged psychotic reactions requiring psychiatric hospitalization, have been reported. Although many users find the experience pleasurable, others become upset and disorganized for several weeks. There are also reports of insidious personality changes in persons who have taken the drugs repeatedly. The magnitude of the abuse and the frequency of the adverse consequences are difficult to estimate.

Simultaneously, there has been an increasing interest in the potential usefulness of these drugs in treating serious psychiatric conditions, such as chronic alcoholism or severe psychotherapy-resistant psychoneurosis and personality disorder. When used therapeutically, the drugs are usually administered in relatively high dosages on one or several occasions. The patients undergo extensive preparation for the experience and are encouraged to utilize it for a reexamination of their personality problems. The patients are also encouraged to expect that the drug experience will be powerfully effective in changing their attitudes, their symptoms, and their way of life. This treatment seems to combine elements resembling religious conversion with intensive goal-directed psychotherapy. Uncontrolled studies report a remission rate in chronic alcoholism running as high as 60 or 70 percent. A recent controlled study reports that 63 percent of the LSD-treated patients had remained "dry" on followups for periods ranging from 6 months to a year and a half. In a control group receiving only psychotherapy and routine hospital treatment from other psychiatrists, only 27 percent were found abstinent on followup. The first grant-supported evaluation of the efficacy of such treatment in chronic alcoholism has just begun at Spring Grove State Hospital.

Methodological development

A number of approaches to the classification of schizophrenic patients into discrete subtypes, presumably more exact and meaningful than the conventional diagnostic subcategories, which are often rather imprecisely used, are being prepared for use with data from the first and second collaborative studies of phenothiazines in acute schizophrenic reactions. Among them are (1) a discriminant function approach developed by a recipient of a career research award at Kansas State University; (2) a profile correlation approach developed by a grant-supported investigator at Catholic University; (3) a typology based on observed differences in patterns of response to drugs, developed by a grant-supported investigator at Hillside Hospital; (4) an approach based on factor analysis, developed by the staff of the Psychopharmacology Service Center; and (5) a novel approach based on patterns of change in individual symptoms, being explored by the staff of the contract-supported biometric unit at George Washington University.

The Veterans' Administration collaborative phenothiazine study group had developed formulas predicting change, with each drug separately, on each of three major superclusters of schizophrenic symptoms (excitement-apathy, schizophrenic disorganization, paranoid process). By applying these equations to data from the NIMH–PSC first collaborative study, the group was able to differentiate patients who would respond best on fluphenazine, as shown by changes in one or two groups of symptoms, from patients who would respond best on chlorpromazine. The results are undergoing further analysis, but the use of common clinical measuring instruments by the Veterans' Administration and the NIMH-PSC studies has already demonstrated its value by showing that findings obtained in a study by one group can be tested on data obtained in a study by the other.

Another interesting approach to data from the first NIMH–PSC Collaborative Study is being explored by a grantee at the University of Miami. This approach, canonical correlation, asks whether any combination of patient characteristics prior to treatment is related to any combination of various measures of improvement. This technique, although developed by a mathematical statistician 30 years ago and described in standard textbooks, has been applied to biological data only infrequently and never to problems in clinical, much less psychiatric, therapeutics.

Because of the importance of clarifying and objectifying psychiatric diagnoses used in the evaluation of drug treatments, the staff of the psychopharmacology Service Center has been collaborating with the staffs of the Biometrics and Professional Services Branches of NIMH in developing a special study of differences in diagnostic practices within the United States and in Great Britain.

BASIC RESEARCH STUDIES

Although many of the findings emerging from basic research studies being supported in areas relevant to psychopharmacology are still difficult to integrate into readily interpretable explanations of the mechanisms of clinical drug action, they do in many cases appear to have an important relation to current problems.

Work by grantees at the University of Oregon and at San Francisco State College is continuing to show that certain stimulants, such as strychnine and picrotoxin, at subtoxic doses, have a novel and interesting effect on the ability of rats to learn complex goal-oriented behaviors. If these drugs are administered just prior to the learning experience, the rats will show superior performance on the task as compared with control groups that received only saline injections during the learning experience. More important, if the stimulants are administered immediately after the learning experience, the rats will also subsequently perform better (and, therefore, appear to have learned more) than saline-treated controls. The effect appears to be on the consolidation or integration of learning rather than on the attention paid to the environment during the actual learning experience. The effect of drug administration after the experience is manifest even if the rats have only been allowed to explore the apparatus and have not actually been trained in it. These phenomena appear to have some relevance to future research on learning problems, possibly even in the area of mental retardation.

A study recently reported by a grant-supported investigator at McGill University in Canada may also serve to elucidate some of the mechanisms of action of chlorpromazine, at least in experimental animals. It has long been known that chlorpromazine will interfere with the ability of animals to respond to a warning signal by, for example, climbing a pole or going into another chamber of the experimental box to avoid the painful shock that always closely follows the warning. Chlorpromazine does not, however, interfere with the ability of the rat to climb the pole or jump to the other half of the cage once the shock has been administered. This phenomenon has usually been interpreted as caused by the anxiety-reducing properties of chlorpromazine, though some research by other grantees has indicated that an alternative explanation might be an effect on the response of the central nervous system to warning signals, making the brain less aware of less important signals but leaving it free to respond to more important signals. In the McGill study, the investigator shows that chlorpromazine's major effect on rat behavior is a slowing of the animal's ability to initiate action following the warning signal. If the time interval between the signal and the shock is short, the rat will look toward the escape route but will not start to move toward it. If the interval between the warning signal and the shock is increased, the rat will get out of harm's way in a purposive and efficient manner. The animal's response to the warning signal is considerably slowed, but the rate at which the animal moves once it starts moving is not different from that of an untreated rat.

A somewhat similar result in the case of human beings is reported by grantees at Boston University. They find that chlorpromazine interferes with a normal subject's ability to react by pressing a button to all the X's occurring at random intervals in a series of many different letters presented rapidly, and one at a time. This is a task requiring rapid reaction to certain types of stimuli inbedded in a much larger number of irrelevant stimuli. Chlorpromazine interferes to a much smaller degree with the subject's ability to perform a continuing though complex coding task in which he must write the appropriate symbols beneath the numbers to which they are paired (the digit-symbol task in the commonly used Wechsler-Bellevue Intelligence Test). Thus the drug appears to impair quick reaction to individual stimuli more than it does the performance of a continuing complex task. It is possible that in the schizophrenic, chlorpromazine may, relatively, suppress intense and rapid emotional responses to minor irrelevant or unpleasant stimuli in the environment while permitting him to carry through with better organized and more purposeful behavior, free from distraction.

At the methodological level, sophisticated methods for measuring behavior coupled with methods for permitting the intravenous injection of drugs through an indwelling catheter into freely moving animals has led to some interesting findings. A grantee at Yale University has reported that rats subjected to unavoidable, painful shock will push a lever to inject themselves with an amobarbital solution much more frequently than will control rats not exposed to pain.

A grantee at Maryland University has employed a similar technique to study the performance of monkeys addicted to morphine. These monkeys can push levers under different signal conditions to inject themselves with morphine intravenously, to obtain food, and to avoid painful shock. When the monkeys are undergoing morphine withdrawal symptoms they are much less able to press either the food lever or the shock-avoidance lever. The most interesting finding to date concerns addicted monkeys that press the morphine lever and receive an injection not of the drug but of saline solution. These monkeys show a prolonged return toward normal in their willingness to work for food or to avoid shock even though their withdrawal symptoms have not been changed by any pharmacological agent.

An old technique, the Lashley jumping stand, has been used by an investigator at the University of Massachusetts to reveal an interesting and unique effect of chlordiazepoxide, one of the newer antianxiety agents. Rats can readily be trained to jump from a stand through one of the two doors that is marked in a distinctive manner, even if the position of the marked, correct door is often changed. The penalty for picking the wrong door is a bump on the nose against the door and a 4-foot fall into a net. If the rat is then exposed to an insolvable problem, by making the differences in the door markings irrelevant, the rat will develop a peculiar, stereotyped behavior, jumping always to one door only, the right or the left, no matter how the door is marked. This behavior will continue after the problem has been made solvable again and the correct door is always labeled the same way. Interestingly, the rat appears to know which door marking is correct. While the animal always jumped to one side, it will jump rapidly if the door is marked with the open sign, and slowly and reluctantly if the door is marked with the locked sign. When chlordiazepoxide is administered during the insolvable problem stage of the experiment, however, it prevents the animal from becoming so fixated that he can never learn a correct response once the problem has been made solvable again. None of the other psychoactive drugs tested had this effect.

In another area of experimental psychology, evidence is beginning to accumulate that responses—shock avoidance or food getting—learned under a given drug condition may appear to have been forgotten if the animal is exposed to the same experimental situation in the absence of the drug. Results of this kind have been reported by investigators both at the University of Rochester and at the University of California at Los Angeles, as well as by an investigator who carried out his research at the NIMH Drug Addiction Research Center at Lexington, Ky. If these findings were to have direct application to clinical drug therapy, they would imply that new patterns of adjustment learned while the patient was under a drug might be abruptly forgotten when the patient was taken off the drug. Clinical observation suggests that this is not the case, although this assumption has not been experimentally tested. These findings may merely reflect the dependence of learning in a lower organism on all aspects of a complex pattern of environmental cues. Human subjects may, presumably, be much better able to distinguish between the relevant and irrelevant aspects of a given learning situation.

At the chemical level, work on the metabolism of phenothiazines and on the development of sensitive and specific chemical methods for measuring the levels of the metabolites in both blood and urine is progressing slowly but satisfactorily. Two of the urgently needed hydroxy derivatives of chlorpromazine have been successfully synthesized after a number of unproductive attempts. The way now seems to be clear for the completion of the synthesis of the several other hydroxy derivatives needed as standard reference agents by grantees studying the metabolism of compounds and the relationship of this metabolism to the compounds' effect in psychiatric patients. A contract-supported study at Southwest Research Institute in Texas has led to the use of tetrahydrofuran, a solvent commonly employed in petroleum chemistry. This solvent makes possible for the first time the complete extraction of polar phenothiazine metabolites from biological fluids. For lack of such a solvent, most earlier work had concentrated on the nonpolar fraction, which constitutes less than a third of the total phenothiazine metabolite content of patients' urine.

A grantee at the University of California has been effectively utilizing both gas chromatography and thin layer gel chromatography for the identification and quantification of opium alkaloids in crude opium samples. These techniques appear to make possible the detailed and specific characterization of opiate samples. This may well permit law enforcement officers of the World Health Organization to identify the geographic source of a drug, thus facilitating control of the international illicit traffic in opium.

Work is proceeding well under two special grants at the University of Pittsburgh and the University of Indiana aimed at developing detailed comparative data on the sensitivity of animal behavioral screening methods to differences among known psychoactive drugs. In another year or so, the available information on behavioral measures as affected by a reasonably wide spectrum of drugs should be sufficient to prove of major value.

A contract-supported group at Hazelton Laboratories is completing a handbook covering the effect of a similar series of standard psychoactive drugs on a much simpler battery of early psychoactive drug screening methods generally used by the pharmaceutical industry. These data will serve as comparison standards for pharmacologists and pharmaceutical chemists who will be utilizing this contract-supported facility to obtain information as to the biological activity of chemical compounds synthesized under psychoparmacology grants or contracts.

Scientific information activities

The extensive file of documents in the area of psychopharmacology encompasses more than 20,000 reprints, manuscripts, monographs, forms, and other materials. These are now being handled as part of the National Clearinghouse on Mental Health Information, with the staff of the Psychopharmocology Service Center serving as consultants to the Clearinghouse staff in this area. An improved coding system for use in retrieving information from this file is being developed by the Clearinghouse staff. Some administrative delay has been encountered in obtaining permission to support, under contract, the more routine aspects of the collection of new documents for this file, their coding and abstracting, the publication of an abstract journal, and the compiling of information requested by the staff of the Psychopharmacology Service Center and other investigators. It now appears that a contract placing both the preparation of the widely read Psychopharmacology Abstract Journal and the management of the document file in a single operation will be let early in 1964. Meanwhile, the staff of the Mental Health Clearinghouse continues to do a remarkable job in providing efficient service.

Three issues of the Psychopharmacology Service Center Bulletin, a newsletter designed to provide rapid communication of all kinds of information to psychopharmacologists, were published in 1963.

The first is a series of several handbooks presenting in concise scientific detail the results of important studies on the effects of psychoactive drugs on animal behavior has recently been published by the Government Printing Office.

CLINICAL NEUROPHARMACOLOGY RESEARCH CENTER

During the past year the Clinical Neuropharmacology Research Center supported by the Institute in collaboration with St. Elizabeths Hospital, District of Columbia, has actively pursued its clinical and laboratory investigations.

In the laboratory research program in the William A. White Building on the hospital grounds, neurophysiologists continue to investigate some of the basic questions of the operation of the brain and nervous system. For example, they are studying the basic mechanisms governing the activity of nerve cells in the brain. Using an exquisitely sensitive technique that permits external application of chemicals to individual nerve cells, the scientists are able to record the electrical activity of the single cells in the brains of animals during administration of the drugs. With this method, they have demonstrated that acetylcholine is not a major neurohumoral transmitter for the activation of respiratory nerve cells, as commonly supposed, but that it plays an important role in the transmission of information within the medullary reticular system.

In another research at the Center, neuropharmacologists and experimental psychologists are studying mechanisms behind the action of psychoactive drugs, their metabolism and their effects on behavior. They have found, among other things, that the hallucinogenic activity of these compounds is strongly dependent upon their conversion to hydroxy-metabolites. Insight into the action of these drugs is sought to refine knowledge of their appropriate use, and to provide information regarding the nervous system structures and processes which affect or determine behavior.

Neurochemists in the same program are investigating stress responses of the sympatho-adrenal system and the biochemical correlates of depression. One project, being carried out in collaboration with NASA, is concerned with stress responses in fliers during space flight. The studies on depression are being conducted in collaboration with NIMH staff in Bethesda. Findings to date have revealed significant correlations between mental state and the metabolism of the catecholamines.

In the St. Elizabeths Hospital building, the clinical research program of the Center is testing a variety of modern treatment methods for mental disorders. The goal is to determine the immediate and long-range effectiveness of new concepts of diagnosis, treatment, and prevention. Two key features of this comprehensive psychiatric facility are a broad range of services, and a flexible system of moving the patient among them, as his needs require. The services include a hospital, a day hospital, a clinic, and a home service.

In the clinical research facility, which formerly consisted only of wards for hospitalized patients, the day hospital has a capacity of 20 patients, and the clinic serves an average of 140 to 150 formerly hospitalized patients. Combined with the home-service program and an emphasis on followup contact with patient and family, the project has made possible the study of patients under widely different circumstances, whether hospitalized or living in the community.

An exhibit, "A Comprehensive Psychiatric Center," describing the clinical research program has been prepared and is being shown at meetings of professional mental health workers. A descriptive brochure is also being widely distributed to psychiatrists, administrators, and other mental health personnel.

It is expected that work in both the clinical and laboratory programs of the Center, in collaboration with the hospital, will continue along current lines during the coming year.

DIFFERENCE IN CHILDREN'S REACTION TO DRUGS

Dr. FELIX. We are finding something very interesting in these drugs. We find that children are not just little adults. Some drugs which are found to be essentially useless for adults are particularly useful in some cases for children with certain kinds of conditions.

Now, this means that we are going to have to go back and do a lot of reevaluation of a number of drugs that have looked as though they did not have much efficacy, they are all right, but there are better ones. But there have been several instances now, and I have them in this briefing document, in which we have found these drugs are particularly good for children.

EMOTIONALLY DISTURBED CHILDREN

Mr. FOGARTY. What are you doing about the problem of the emotionally disturbed child?

Tell me, what is your definition of an emotionally disturbed child?

Dr. FELIX. An emotionally disturbed child—first, let me tell you what it is not, so then I can better tell you what it is.

An emotionally disturbed child does not mean a child who is necessarily physically disturbed so he is running about and screaming and yelling. An emotionally disturbed child is a child emotionally ill to the degree that he cannot communicate effectively nor relate well socially to parents or to playmates. The child will not be able usually to adjust satisfactorily in school. Often he will not be able to take direction or discipline from parents.

Disturbance can take one of several forms. The child can be so withdrawn he behaves almost like a vegetable. In many cases the child may be misdiagnosed as mentally retarded. This is one of the reasons why, as we have divided up on the basis of what our various functions are, our roles in the mental retardation field, it has been agreed that the Institute of Mental Health must be concerned with the problem of differential diagnosis and secondarily concerned at least with the problem of learning because of what this means in terms of the disturbed child, and also what the whole area of cultural deprivation has to do with it.

The child, on the other hand, may be aggressive in bizarre and blood-chilling ways, for instance, the child may be almost homicidally disturbed and will attack other children viciously.

The child, on the other hand, may be overactive without attacking, always doing something, never still a moment. And there is often no way of getting through to such children. They are heartbreaking little fellows, absolutely heartbreaking. So much so that one of our most serious problems, next to the adolescents which I mentioned earlier, is to get people trained to deal with these children and get them to stay with the children. That is, they will start out as child psychiatrists, but pretty soon they drift over to adult psychiatry. I am a glaring example of this. I started out to be a child psychiatrist. I do practically nothing with children now because it has gone beyond my competence in many cases. I deal with adults much more. Children are emotionally very taxing, they are frustrating, they are difficult. But child psychiatry is an essential aspect of the whole field of psychiatry.

RESEARCH ON EMOTIONALLY DISTURBED CHILDREN

Mr. FOGARTY. What are you doing about this problem?

Dr. FELIX. Our child research unit is carrying on a number of studies, part of which I described a moment ago. There are other studies being carried on by another group on family therapy, in which in the case of these children the total family is being treated.

We have a number of grants operating at the present time in various parts of the country, I mentioned earlier, I believe, in my opening remarks.

Mr. FOGARTY. What do you mean by total family? Is it necessary to treat the total family in many cases?

Dr. FELIX. Very frequently it is. And the reasons are several. The child's problem may stem from very deep and malignant problems in the family, or the child may create problems in the family by virtue of his sickness. And you do not know which comes first, the hen or the egg. You have to separate them out.

There are a number of studies being carried on by grants. I have mentioned earlier the work that has been done by use of drugs in disturbed children, I think in my opening comments.

Another one I mentioned in the past here is the study that was carried on in Texas—this was a title V project, too—in which youngsters who were so disturbed they could not go to school were brought in with their parents for 3 days every 6 weeks and they were given very intensive therapy, the whole family. On the basis of this, over half of these children—it was possible in over half of these cases for the children to return to school.

Now, this is not ideal, but, as you know, Mr. Chairman, one of my great concerns has always been what do you do for the folks out in the country? I come from a rural area, and I am never able to quite forget that it is easier to get things in the city than in the country when you live 30 miles from town. So this has been one project dear to my heart. How do the folks out in the country get to avail themselves of some kind of care and treatment?

There have been a number of studies carried on. One of them was at the Menninger Clinic, Topeka, Southard School of the Menninger Clinic, how normal and abnormal children cope with various situations. What is the difference? How do they deviate? How can you correct it? If you wish, I can develop this further.

Mr. FOGARTY. I wish you would.

(The information requested follows:)

SPECIAL REPORT: EMOTIONALLY DISTURBED CHILDREN

INTRODUCTION

The conquest of emotional illnesses in children continues to be one of the major goals of the National Institute of Mental Health. This is reflected in the Institute's heavy investment in research aimed at the solution of the difficult and varied problems of child mental health; from its inception in 1948, NIMH has devoted between one-fourth and one-third of its annual research grant program to studies dealing with mental health in children—or, more specifically, to both basic and clinical studies aimed at improving our understanding of the etiology, diagnosis, treatment, and prevention of intellectual and emotional disorders suffered by children.

The concern of NIMH with children springs from an awareness of the toll taken by the mental and emotional disorders in the early years of life. Such disorders, like those in the adult, may take the form of psychoses, neuroses, or psychosomatic disorders; they may be reflected in retarded mental development, or evidenced in delinquent behavior. An estimated 10 percent of public school children in the United States are emotionally disturbed and in need of psychiatric guidance, and at least 250,000 children with less serious psychiatric disorders receive treatment each year at mental health clinics.

For purposes of research, diagnosis, and treatment the Institute considers childhood as ranging in age from the neonatal period through adolescence. The emotional disturbances of these children can and do range from minor behavioral disorders to severe psychotic episodes and juvenile delinquent behavior. The forces which mold and act on, and through, the emotionally disturbed youngster are organic, psychological, and social. It is appropriate and essential therefore that NIMH concern itself with these various forces which either individually or in combination produce emotionally disturbed behavior among our children and adolescents.

INTRAMURAL RESEARCH ON DISTURBED ADOLESCENTS

Adolescence is a period marked by rapid changes in behavior which are determined by psychological maturation and by new social expectations; adolescence is also a period of vulnerability to serious personality disorders. It is the general goal of NIMH studies of personality development in adolescence, therefore, to investigate the basis of psychiatric disorders during this period.

One project involves an interview study of the family of the disturbed adolescent to determine the relationship between the personalities of the parents and the development of emotional disturbance in the adolescent. The study is based on a central thesis of dynamic psychiatry; i.e., that there is a relationship between the personality development of a child and the personality of the parent. The NIMH project involves the creation of an experimental situation in which to test this thesis, and to demonstrate the specific qualities of parent-child relationships which are related to specific personality development in the adolescent.

A group of adolescents has been hospitalized who have had severe emotional breakdowns in the period of their first separation from their parents during the first year of college. Investigators are identifying the specific personality difficulties of each adolescent, and then relating these to the characteristics of the adolescent's family relationships.

The parent-adolescent relationship is studied in a weekly group session conducted by a psychiatrist and a psychiatric social worker. The hour-long session involves the adolescent, his parents, and any adolescent siblings in the family. The session is observed by the research team and is recorded, and it is these observations and recordings that serve as the data from which deductions about the nature of the parent-adolescent relationship are made. Each adolescent is also treated in individual psychotherapy, is interviewed by research personnel, and is given psychological tests; the assessment of various aspects of his personality is made from these data. With these data, the investigators seek to establish the relation between the individual psychology of the family members,.and their impact upon each other—with particular emphasis on the impact of various aspects of the parent's personality on the developing adolescent.

Data regarding the parents of the patients reveal them to be uniformly disturbed individuals, whose marriages are fraught with difficulty and who frequently have difficulties at work. They are found to be highly anxious persons, deeply concerned about their own adequacy in coping with life's problems. Often they have had experiences of great difficulty in their own adolescence, and their anxious interference with the patients' adolescent adaptive efforts seems to reflect the parents' own areas of conflict.

Because the parents themselves are exceedingly insecure, they manifest an inability to tolerate independent thinking and action on the part of the developing adolescent—as if such behavior were a challenge to their precarious self-esteem. What emerges is behavior designed to control and mold the adolescent in ways which will not threaten the parents' authority and their preconceptions. The parents also exhibit a type of competitive behavior toward the maturing adolescent. This competitive response on the part of the parent is often threatening to the adolescent and inhibits his attempts to achieve more mature satisfactions. Such parents often have extremely pessimistic expectations of what tasks the adolescent can master and accomplish with success. The pessimism seems in part to reflect competitive attitudes toward their children as emerging adults. The more complex dynamics of this pessimism seem to indicate an inability by the parents to psychologically distinguish their children from themselves, as they project their own anxiety and low self-esteem onto their image of what the children might be and do. The result is often that the adolescent "freezes" at a level of behavior dictated more by the parents' anxieties than the child's capacities.

In this research with the family groups the investigators are also interested in developing new techniques of family group therapy which will provide a more effective treatment of disorders of adolescence than presently exists.

EXTRAMURAL RESEARCH ON DISTURBED ADOLESCENTS

Well over 500,000 children are brought before the courts each year for the kinds of antisocial acts we recognize as juvenile delinquency, with many of the children suffering from emotional disorders directly reflected in their behavior; last year, while the number of American children in the 10-to-17 age group increased by 3 percent, the number of juvenile delinquency cases in this same age group rose by 10 percent. And, although a drop in the number of total patients in mental institutions is expected by 1970, the number of patients in the 10-to-24 age range is expected to increase. Clearly, major strides are yet to be made in combating mental illness among the younger age groups.

During fiscal year 1963, a total of over 200 research grants for over $6 million were awarded for projects dealing directly with the study of emotionally disturbed children; this represents roughly one-eighth of the total number of projects and the total amount awarded during the year. (This body of work does not include those essentially basic, normative studies of the emotional and intellectual development of children which represent an equally sizable portion of the overall NIMH research program.) Represented here is the work of investigators in the biological, medical, psychological, and social sciences in studies covering such varied fields of study as neurophysiology, genetics, learning, motivation, perception, cognition, language, family processes, and the community—to name but a few.

A substantive overview of the Institute's research effort to solve problems of emotional disturbances in children follows. While the groupings of projects under specific headings are arbitrary, they are presented to indicate the general scope of the research program in the field; the specific projects cited should be regarded only as illustrative of many others like them.

Most of the studies described here are quite clearly clinical in content, focusing on specific psychopathological phenomena; it should be understood, however, that progress in the understanding and treatment of mental illness—in children as well as adults—depends in the final analysis on a vast accumulation of knowledge regarding the fundamental mechanisms involved in behavior and its development.

Basic behavioral research with children is therefore considered an important and integral part of the overall NIMH program in child mental health. Studies of the language of schizophrenic children, for example, are meaningless unless we know more about the child's language development in general; studies of the perceptual distortions of schizophrenic children do not make much sense unless we know more than we do now about the parameters of the normal child's perceptions; and learning problems of retardates are meaningful only in the context of learning studies of normals. We know, too, that the key to the emotional adjustment of the adult lies in his early childhood. Current theories of neurosis stress the importance of events in early life; indeed, the origins of the most severe mental disorder of adulthood, schizophrenia, may lie, for example, in the earliest relationship of mother and child. And, it is the process of education and socialization of the child which maintains the health and continuity of our society, and transmits the best (or worst) of our culture from one generation to the next.

Although basic studies in areas like those noted above are not reported here, they continue to provide the groundwork for productive clinical research with the emotionally disturbed child.

EMOTIONAL FACTORS IN JUVENILE DELINQUENCY

Because many juvenile delinquents suffer from emotional disorders, a good deal of research is being devoted to the as yet unestimated contribution of emotional factors to delinquent behavior.

A number of investigators are concerned with analyzing the sources of aggressive, antisocial behavior in children. As part of an important study of imitation as a factor in social learning, for example, one grantee reports that children who are exposed to aggressive behavior by adults—whether the adults are in the flesh or on a TV screen—are more likely to turn to aggressive behavior themselves.

In recent experiments, children have been placed in the company of persons exhibiting certain types of behavior; then the children have been observed to learn to what extent they reproduce this behavior. Sometimes films have been used, projected on a screen in a television console. Aggressive behavior on the screen is found to be even more influential than the same behavior by the same adults in real life. The investigators also report an experiment showing that a child tends to change the pattern of his moral judgments to accord with that of an adult model. Much of a child's social behavior, the grantee sums up, is acquired through imitation of adult models.

Another investigator interested in the sources of aggression has provided some of the first evidence as to the effect of TV programing on real-life behavior. The grantee reports a significant positive relationship between the violence of favorite programs as rated by the parents of third-graders and the aggressive behavior of third-grade boys as rated by their classmates. But the relationship between time spent watching TV and aggressive behavior is negative. In other words, as the amount of violence increases, the aggression rate increases also, but as the amount of time spent in front of the TV goes up, aggression ratings go down. In the case of girls, no significant relationships were found. The grantee, while pointing to some unanswered questions, is inclined to believe that TV viewing affects real-life behavior and that the modeling variable is a crucial one.

One group of social scientists has studied the family backgrounds of men who were equally aggressive in childhood but only some of whom became antisocial; the subjects were 255 men who had been observed with their families for 5 years during childhood and early adolescence. The investigators classed them as antisocial if court records showed a conviction for larceny, breaking and entering, assault, or sex crimes. Half of the aggressive adolescents, it turned out, had no records of antisocial behavior.

Within our society there is considerable evidence that crime and delinquency are associated with the failure to give a boy adequate opportunity to identify with his father (though this failure cannot be the whole answer because it does not inevitably lead to a bad outcome). A cross-cultural study supported by an Institute grant finds that the same is true in many other societies. The sample comprises 48 nonliterate societies selected on the basis of geographical diversity and on the adequacy of information concerning (*a*) aboriginal child training practices and (*b*) criminal behavior. A high frequency both of theft and of personal crime, the investigators find, tends to occur in those societies where the young boy is limited in forming an identification with his father.

Some preliminary findings by a grantee who is making a detailed study of street corner groups and gangs illustrate the complex nature of the delinquency problem. For example, such images as "someone who works for good grades at school," "someone who reads good books," and "someone who saves his money" are very positively evaluated by gang members. Yet the grantee notes that with rare exceptions these boys drop out of school early, read almost nothing, and spend, almost immediately, any money they acquire.

A number of lower class Negro gang boys, interviewed individually, almost unanimously said they expected for themselves marriage, small families, hard work, and thrift. In a group session, however, the same boys derided anyone who practiced these virtues. Thus, the investigator points out, group pressure and expectations operate to define for the individual what is acceptable behavior in the group. But other influences must operate, too, to create the discrepancies between individual values and behavior. For instance, within 18 months after these boys had individually espoused middle-class family attitudes, a high proportion had had an illegitimate child—an occurrence, the investigator reports, having nothing to do with group pressure.

As for criminal activities, these seem to be characteristic of individuals and cliques rather than of gangs themselves.

The gangs being studied are those with which the YMCA of Metropolitan Chicago has been working. In the case of a number of these groups, the grantee reports, gang fighting has been almost eliminated. The researchers want to learn why this has happened and why other forms of delinquent behavior seem much more resistant to change.

A number of Institute grantees are concerned with finding more effective ways of treating adolescent delinquents. One recently completed study deals with a cottage that housed 70 of the inmates of a large institution. When the boys left, they were generally more hardened and exploitative than when they had entered. The study points toward the desirability of the types of facilities and programs being tried in several correctional systems in this country; smaller, simpler institutions; small cottage groupings of 20 to 25 boys; and sufficient personnel to carry out intensive treatment and activity programs.

Institutionalized delinquent boys receiving dextroamphetamine, an antidepressive, were observed by another NIMH grantee and his colleagues to show marked improvement in behavior. Further, there was a general improvement in behavior among all the boys in each cottage, and this the investigators believe probably resulted from a more harmonious atmosphere secondary to the behavioral improvement in the drug-treated cases. The research team points out that (1) if a delinquent youngster can establish better relations with training school personnel, a more constructive outcome of his period of commitment may result and (2) those better relations presumably will be facilitated if his behavior improves. Further systematic study of the effects of psychopharmacologic drugs and other factors in the training school environment are needed.

CHILDHOOD SCHIZOPHRENIA

Schizophrenia remains the most severe psychiatric disorder among children as well as adults—and the least well understood. Typical of many young schizophrenics is autistic behavior, a complete withdrawal from the world which often first appears in early childhood or infancy. Such behavior is generally regarded as the earliest form of schizophrenia; it is also the most poignant, for it represents a portent of the waste and suffering of adult years to come.

One long-term project begun in fiscal year 1962 involves research—including longitudinal studies—on the etiology and epidemiology of childhood schizophrenia. The reesarch team will continue some of its earlier work dealing with the development of neurologic and psychiatric criteria for the appraisal of schizophrenic children, and the analysis of prenatal and perinatal factors in the etiology of the disorder; the investigators will also initiate a number of additional projects, including a study of developmental changes in the treated schizophrenic child based on analyses of the features of the child and his family that correlate with clinical progress, and comparisons of the relative effectiveness of day and inpatient treatment. As another element of the overall project, the investigators are assessing the families of schizophrenic children; their aim here is to collect information on the incidence of psychosis among the parents and siblings of schizophrenic children, and to test the hypothesis that the term —"childhood schizophrenia"—subsumes a heterogenous group of patients with a complex etiologic spectrum ranging from somatic to familial factors.

Investigators continue to regard as crucial the role of psychological, social, and cultural factors in the etiology and course of childhood schizophrenia. A number of projects supported by the Institute, for example, are designed to study the impact of the family on the evolution of schizophrenic illness. Noting the evidence that schizophrenic patients tend to come from seriously disturbed homes, one research team has intensively studied 16 families having a schizophrenic child and at least one other child. The question was why one child had become schizophrenic and not the others.

The findings, however, do not show the siblings of schizophrenics to be entirely free from mental illness. Among the 24 siblings of the patients, as many were found to be psychotic as reasonably well integrated, and all except 5 or 6 suffered from serious personality disorders. A definite sex linkage is reported; only one sibling of the same sex as the patient was considered to be reasonably stable, and no sibling of the opposite sex from the patient was found to be overtly psychotic. The researchers report that the demands of development confronting children of opposite sexes in a given family were very different, and that even those close in age had been subjected to quite different intrafamilial influences.

In another study, the investigators have focused on birth order as a variable related to the course of schizophrenia. More patients (both recovered and unrecovered patients in State hospitals) were found among the younger rather than the older siblings in large families (five or more children); the tendency was more marked for the females than for the males. The investigators suggest that a large number of older siblings increases the likelihood of schizophrenia; they report, too, that patients with a large number of older siblings seem less likely to recover than those with few.

The data of this study, while providing evidence that birth order is related to the incidence and prognosis of schizophrenia, do not clarify the specific reasons for the relationship. For example, it is possible that a consequence of a large number of births is a detrimental change in the intrauterine environment, especially in association with advanced maternal age. But it seems more consistent with available information about schizophrenia to look for the responsible causes in the patient's family environment. The presence of a large number of older and therefore more capable siblings in the family may be the occasion for considerable stress—especially in combination with the inadequacies reported as characteristic of parents of schizophrenic patients.

In spite of the many difficulties in this area, the interest in defining the relationship between early family influences and the development of emotional difficulties and mental illness can be expected to grow. Among the difficulties, investigators themselves point out, is investigator bias—an unconscious tendency evidenced in many areas of research, to find in a given situation what one is looking for. One grantee believes that the time has come for a long-term predictive study. In such a study, to take an oversimplified example, if condition X in a family is thought to be necessary for the development of schizophrenia, the researcher will predict that if X (along with other specified conditions) is present, a child in the family will become schizophrenic some years hence; and that if X is not present, none of the children will become schizophrenic. A pilot study to develop a methodology for such a long-term investigation is underway.

In the treatment of childhood schizophrenia, the problem of drug therapy is a difficult one, for the differential application of drugs must be made carefully in terms of subtle differential diagnoses.

In order to get a trustworthy measure of a drug's effect on emotionally disturbed children, one investigator has found it necessary to divide such children into four general groups: (1) severely impaired schizophrenic children; (2) a borderline group, less severely impaired at present than the children of the first group; (3) children with predominantly neurotic manifestations—anxiety, and feelings of helpless dependence and inadequacy; and (4) children with predominantly sociopathic or paranoid features who tend to deny personal responsibility for their feelings and acts.

In a pilot study, most of the more severely disturbed children—those in groups 1 and 2—improved on chlorpromazine, a widely used tranquilizer; about half improved on another drug; none improved on a placebo treatment. Among the other children, however, the effectiveness of chlorpromazine—in terms of the percentage of children who improved—differed little from that of a placebo. Improvement in the first two groups, then, seems to depend primarily on the effectiveness of the drug being studied; in the second two groups, upon such factors as hospitalization, psychotherapy, special education.

The grantee's research team has confirmed that a child's response to a psychiatric drug may be quite different from an adult's. For example, trifluoperazine, a tranquilizer having less sedative action than chlorpromazine, has been found to be a stimulating agent when given to retarded schizophrenic children and to be capable, on the basis of preliminary findings, of bringing moderate improvement. Other drugs are being tried in the hope that even more potent agents will be discovered.

The investigator estimates that at least 60 percent of severely disturbed children can be moderately improved by presently available drugs. Among children in an outpatient population who were too disturbed to benefit from psychotherapy, drugs enable one-fourth to go to regular schools and another one-half to participate in group activities and special classes.

Special screening of drugs potentially valuable for disturbed children is essential, the grantee reports, because a drug's action may depend upon the stage of the child's development. Quite possibly, drugs that are ineffective in adult animals or human beings may prove valuable for children.

The investigators also point out that dosages of psychopharmacologic drugs must be determined separately for children and not merely adjusted from adult dosages according to body weight. A dosage that has been scaled down in this manner may be so high for a child as to cause toxic symptoms. Or, it may be so low as to be ineffective.

In another study, the aim is to see whether psychotic children who would ordinarily be referred to institutions can continue functioning in their own homes through the use of a tranquilizing drug. The plan is to study two groups of children over a 26-week period; one group will receive a tranquilizer in appropriate regular doses while the other group will receive a placebo.

One of the clinical research centers supported through the Institute has as its basic mission the conduct of studies in the etiology, pathogenesis, clinical phenomenology, and efficient therapy of the young schizophrenic child. The research projects now in progress include precise objective descriptions of the child's behavior in relation to people and objects; physiological and neurological studies of the status of the endocrine and nervous systems of these children; clinical studies of the critical antecedent conditions producing clinical symptoms; and studies of a variety of treatment procedures. In one of the treatment studies, for example, reinforcing techniques, widely used in studying animal behavior, will be applied to an analysis of the capabilities of autistic children. In general, under these techniques, a subject learns that behavior desired by the experimenter is followed by a reward. On the basis of his early results, from work with two severely disturbed children, a grantee finds that the behavioral patterns of such children can be broadened. Except in the rate at which these children acquire new types of behavioral control, the results to date suggest no basic deficit. The hope is that if behavior repertoires can be significantly widened in the experimental room, ways will be found of helping these disturbed children change their response to real life situations.

One of the challenges to those doing research in schizophrenia lies in the difficulty involved in reducing complex symptoms into meaningful diagnostic categories; a number of projects are directed at resolving this problem. Investigators also continue to probe the abnormal intellectual, cognitive, and perceptual processes of the schizophrenic child in order to determine their role in the disease process.

One team, for example, has been engaged in attempts to clarify the difficult differential diagnosis between childhood schizophrenia and retardation among preschool, preverbal children. Psychological tests have revealed a greater variability in the intellectual functioning of the schizophrenics; the results indicated, too, that the schizophrenics are especially impaired in specific areas, including language and toilet training habits, while the retardates showed no specific disabilities. Results after a year of psychotherapy indicated significant gains for both the schizophrenics and retardates; contrary to expectation, the retarded children made more substantial gains. A control group comprised of schizophrenic children receiving no therapy showed evidence of regression.

The importance of gross cognitive and intellectual impairment in childhood schizophrenics has been noted by many. The literature concerned with the effects of schizophrenia on intelligence, however, although voluminous, is highly contradictory; a major problem is the lack of objective data on the premorbid intellectual ability of the schizophrenic. In one project, therefore, investigators have correlated measures of intelligence taken of children in the elementary school with similar measures taken more recently when, as adults, they became ill and were admitted to a mental hospital. Initial data point to the finding that certain progressive deficits in intelligence appear in children before they exhibit overtly schizophrenic symptoms; second graders who were not diagnosed as schizophrenics until adulthood were already significantly below their own siblings in intelligence.

Because the development of speech and language reflects so strongly various elements of personality, a fuller understanding of childhood schizophrenia is being sought by a number of investigators through the study of linguistic phenomena. In one project, for example, the primary object is to explore the language comprehension and speech behavior of a group of autistic children. Vocalizations and verbal output will be tape recorded in various situations for phonetic analysis, and language comprehension will be explored by means of a specially developed scale. In another project, the purpose is to investigate the verbal behavior of schizophrenics (adults as well as children) as contrasted with normal controls in order to determine the variables.

A variety of leads are being explored in small pilot studies. In one project, for example, the investigator is studying autistic phenomena in congenitally blind children: careful observations of these children and their mothers might enable us to better understand the phenomenon of autism, for there is some evidence that autistic patterns in the congenitally blind result not only from the child's early experiential deficit, but also from the mother's inappropriate modes of adaptation to the child's plight.

THE RETARDED CHILD

The field of mental retardation has long been one of the central mental health concerns of NIMH. Recently, with the establishment of the National Institute of Child Health and Human Development, a variety of projects in mental retardation were transferred from NIMH to the new Institute—primarily those dealing with biological and hereditary factors in the etiology of retardation. However, as part of its major concern for research on childhood emotional disorders, the Institute does continue to maintain a strong programmatic interest in retardation, focusing on three major areas: studies of psychological and social processes in the retarded—including, for example, studies of learning, personality, and character development, and of the etiologic role played by such psychological and social factors as emotional and cultural deprivation; studies of the adjustment problems of the retarded—including research on the stressful influences which the retarded child's presence generates within the family, and on the diagnosis, prevention, and treatment of behavioral disorders from which the mentally retarded frequently suffer; and studies of the care, management, and training of the retarded in institutional and community settings.

One investigator, who has been working in the field of retardation since the late 1930's, is at present conducting a study to determine whether foster home care will overcome the retarded behavior of children reared in an institution for infant care. A comparison will also be made between the behavioral development of children reared in homes and those reared in institutions. Another study has recently been begun, which is expected to contribute significantly to information in this area; here, a research team in Israel is investigating the interaction between infant environment and subsequent social learning in children from three types of home environments: a residential institution, a collective settlement, and middle-class families.

Many laboratory studies are being conducted of early handling and deprivation. These studies show the effects of sensory deprivation and social isolation on perceptual, emotional, and intellectual development. Certain salient characteristics of deprived infants were found to be a failure to perceive and respond to environmental cues, even pain; an extremely high level of excited behavior; and a low capacity for learning new responses in problem-solving situations.

There is a commonly held, though often disputed, view that a retarded child differs from other children in certain immutable ways over and beyond his intellectual deficit. Part of the evidence for this view lies in experimental results showing a more rigid behavior by retardates than by normal children of the same mental age on concept-switching tasks (such as grouping objects by color and then noticing that they can be grouped by form, too). Recent work with middle-class normal children, lower class normal children, and institutionalized retarded children—all three groups having the same average mental age, 6.9 years—indicates that the results of such an experiment depend upon how the subjects are motivated. Middle-class children, the NIMH grantee theorized, would perform more effectively when given an intangible reward—simply the instructor's voiced approval for having done the job right; on the other hand, lower class children and retarded children would do best when offered a tangible reward—tokens to be exchanged for a prize. When each group received its own best reinforcer, the researcher predicted there would be no difference among the three in their ability to switch concepts. In general this proved to be so.

Research with retarded children, the grantee emphasizes, must allow for the social deprivation and other differentiating factors in their experience. Their rigid behavior in certain situations—for example, their perseverance in playing a monotonous game—is due not to innate rigidity but to a heightened desire, springing from social deprivation, for the support, approval, and continued attention of the adult observer.

Recently, a large program project was begun to establish a clinical research center for the treatment of mentally retarded and emotionally disturbed children. The investigators will conduct a comprehensive program of research of the disabilities in learning and in social interaction that are experienced by retarded and disturbed children; the research center will be a component of a new State institution for children.

Through a special 5-year NIMH research grant, some 4,000 mentally retarded hospital admissions during 1945–60 are being individually studied in terms of physical, mental, and behavioral characteristics before, during, and after hospitalization together with the medical and social characteristics of their families. Special scales are being developed to correlate the behavior, capabilities, and social and psychological problems of the patients with events surrounding hospitalization and discharge. The findings are expected to sharpen prognostic techniques, to furnish bases for hospital and community program development, to increase understanding of the natural history of mental deficiency, and to supply source data for further medical, psychological and sociological research.

In the past year, the same investigators have begun a large-scale study of the retarded in the community. They plan to investigate the prevalence and the process of identification of mental retardation and, also, to study the natural life histories of the retardates and their families.

MISCELLANEOUS CHILD BEHAVIOR DISORDERS

Many children display abnormal behaviors which, though not severe enough to be classified as psychoses, nevertheless pose serious problems. Among these, for example, are abnormal fears of school, learning problems, speech problems, and—in general—behavior that might be termed "neurotic."

The importance of childhood environment in later development and adjustment has long been stressed in theory, or with the evidence of abundant case histories. One investigator experimenting with monkeys provided the first important corroborative scientific evidence that inadequate rearing and traumas such as social isolation do, in fact, disrupt normal behavioral development and lead to difficulties comparable to the personality disorders and severe mental illnesses encountered in humans. In one series of studies, for example, it was shown that infant monkeys who are separated from their mothers at birth and deprived of physical contact with other animals develop bizarre behavior patterns—from mute withdrawal to frenzied rage. It was demonstrated, too, how the capacity to learn and to relate in others in a group is affected by childhood experience. In recent investigations, it has been shown that monkeys who suffer early psychological trauma such as the deprivation of maternal protection and warmth grow to be inadequate and unworthy parents themselves; the investigator reports that these monkeys, "having never known a real mother themselves, become helpless, hopeless, heartless mothers devoid, or almost totally devoid, of any maternal feeling." The concepts and methods developed in this research have already been applied by several research psychiatrists and other behavioral scientists in clinical investigations and have been found to be of great importance.

Two child clinics are engaging in such research studies. One group of investigators is selecting for study families who have one disturbed child and an adjusted sibling of the same sex. They are studying the role of the parents in the development of psychopathology in the child, and they are particularly interested in comparing the parents' interactions with the disturbed child and with his adjusted sibling. Repeated observations will be made of parent-child interactions which are believed to contribute to the child's pathology. The investigators expect that as the quality of these interactions change, improvement will be observed in the child.

A second large study being conducted at a child clinic also has as its goal the identification of family stresses which may be specifically related to a child's neurotic behavior. The investigators hope to manipulate these emotionally disturbing individual and family stresses to the therapeutic advantage of both.

Special emphasis has been placed in recent years upon language disorders, particularly delay in development, defective articulation, and stuttering. One investigator has explored both the etiology and treatment of such disorders. She has found that the disruption of mother-child relationships during a period of intensive language learning is often reflected in the development of language disorders. She has developed a system which describes the stages of language development from birth to adolescence and the mother's role in each stage of the development. Her system also includes means of selecting therapeutic methods, based on the age of the child and the type of language disorder. Both mother and child are included in the treatment process. The most promising results have been achieved with very young children.

Another investigator has found that the speech of the anxious child can be distinguished from that of the nonanxious child by its lower comprehensibility and other factors. In evaluating a child's intelligence, ability, and other traits on the basis of his verbal facility, investigators ask, do we not place him in a vicious circle? If he becomes test anxious, his speech behavior and, consequently, the evaluation will be affected. Sensitivity to a poor evaluation may serve to increase his test anxiety and thus lead to further disturbances.

In working with third graders, these researchers find that some children who are truly anxious are rated "low anxious" on a test scale because their anxiety is masked by defenses. Hence, in measuring anxiety in children, a correction factor for defensiveness must be included.

Two investigators have been conducting stimulating research on the causes and control of emotionally disturbed children in the regular classroom situation. One investigator points out that although authorities from various disciplines recognize the importance of the school and classroom teacher in the life of the emotionally disturbed child, there are no definitive research projects devoted to the problem of what the classroom teacher can do in the way of programing for, or in managing the behavior of, emotionally disturbed children. His research will focus on the practical problem of what the classroom teacher can do or avoid doing in the way of programing, teaching, and managing the behavior of emotionally disturbed children in the classroom.

Another investigator has applied operant conditioning techniques to modify the undesirable behavior of moderately disturbed nursery school children. In each of the cases studied so far, the deviate behavior was readily altered by social reinforcement from the teacher. The investigator suggests that some traditional methods used by teachers to handle behavior problems may have strengthened the misbehavior rather than have eliminated it. Further studies will be concerned with the stability of the improvement in the child's behavior. The investigator also hopes to extend his work to more severely disturbed children.

Clinical and basic studies of emotional disorders in children are supplemented by research to improve the diagnostic procedures in child study. A group of investigators has developed a method to measure objectively the general activity level of children. The concept of hyperactivity plays an important role in the diagnosis of behavioral abnormalities in children. Hyperactivity, in the clinical sense, refers to an abnormal amount of motor activity on the part of the child. In its extreme form it interferes with the child's functioning and handicaps him in learning situations. Hyperactive children present a most difficult problem for parents and for teachers. Present methods of working with these children are drug therapy and environmental adjustment. Now that these investigators have perfected a method for measuring hyperactivity they intend to explore in a more meaningful and reliable manner the effects of therapeutic techniques in modifying the child's motor behavior.

Another investigator has developed a complex instrument for measuring changes in the mental health status of children undergoing psychiatric treatment. The instrument measures specific life tests that must be achieved by a child in any culture—i.e., significant aspects of the child's interaction with adults and peers. Hopefully, this instrument will be both a valuable diagnostic tool and one which can be used for evaluating the therapeutic process.

PROFESSIONAL AND TECHNICAL ASSISTANCE

There is increased concern in the States and local communities over mental illness and other disabling psychiatric disorders among children. This concern is accompanied by an intensified search for causes and for better methods of prevention and treatment.

Statistical data on the number of emotionally disturbed and mentally ill youngsters in the country and for those receiving care and treatment are incomplete. For fiscal year 1962, the Biometrics Branch of the NIMH estimated that there were 3,500 first admissions of youngsters under 15 to State and county mental hospitals. The few private hospitals serving these youngsters admitted another estimated 400. It has been estimated that at the end of 1962, about 5,000 youngsters under 15 were resident patients receiving either intensive treatment or prolonged care in these institutions. About another 5,000 were in care in private residential treatment centers, foster care institutions, and institutions for juvenile delinquents.

Regrettably, only a small number of States have both the facilities and available specialized staff to provide separate wards or units for emotionally disturbed youngsters in the State hospitals. During the current legislative year, a number of States appropriated funds for the construction of new units or the renovation of existing facilities to provide separate treatment facilities and programs for youngsters.

Few emotionally disturbed or mentally ill youngsters are in need of inpatient care. As community psychiatric resources continue to expand and with the development of the comprehensive community mental health centers, more and more of these youngsters will be able to remain with their families while under treatment, or be returned to them at the earliest possible time.

In fiscal year 1962, an estimated 270.000 youngsters under 18 years of age were under care in outpatient psychiatric clinics. For every 100,000 youth in this age group in the United States, 403 were seen in clinics during the year. Of the total number under 18 seen by clinics, 213,000 were under the age of 15.

Outpatient psychiatric clinics serve more patients in the adolescent ages than in any other age group. In fiscal year 1962, an estimated 123,000 boys and 71.000 girls, a total of 194,000 adolescent patients 10 to 19 years of age or 623 patients per 100,000 population were seen in clinics. This number accounts for more than 25 percent of the nationwide clinic caseload.

Because of the interest in this large group of clinic patients, a special study on the characteristics of adolescents and their clinic experience has been conducted by the Biometrics Branch outpatient psychiatric clinic reporting program. Nationwide data have been collected for male and female patients, by 2-year age groups from 10 through 19 years of age, terminated from service in 1962. The services and disposition of these patients will be studied in relation to source of referral and diagnosis. Thus, differences in problems, needs, and utilization of clinic services will be analyzed for persons who are in preadolescence, early adolescence, middle adolescence, late, and post-adolescence.

A preliminary analysis of the data indicates that the schools accounted for the largest proportion of referrals of the 10–15-year-old age group to clinics (more than 30 percent) ; the largest proportion of referrals of older adolescents was from their families or were self-referred. Only a third of the patients received treatment; the remaining two-thirds received other services such as intake, diagnostic, or other nontreatment services. The largest proportion of young adolescents received a diagnosis of transient personality disorder; older adolescents were diagnosed as personality disorders. Passive aggressive personality disorders, schizoid personality disorder, and anxiety reaction were the specific disorders most frequently diagnosed. Approximately 25 percent of all youngsters were diagnosed as psychotics and treated in clinics, and almost 50 percent of those receiving services other than treatment were referred to inpatient facilities.

A major mission of the Institute is to assist States and local communities to develop necessary services for emotionally disturbed children. The comprehensive community mental health centers will be very important in this regard. In the meantime, there is need to identify and list those services which already exist and make them known. This will enable parents of these children, professional people, and private medical, and welfare agencies to make the maximum use of them. For several years, the Institute, in cooperation with the National Association for Mental Health, has been publishing a yearly directory of outpatient psychiatric clinics. The 1963 edition will also include psychiatric day-night services.

For the first time, a "Directory of Resources for Mentally Ill Children in the United States" was published early in 1934 through the cooperative efforts of the Institute and the National Association for Mental Health. This directory lists public and private day and residential treatment services for youngsters.

STATE AID

The NIMH devotes a major and significant portion of its program activities in behalf of the prevention, detection, diagnosis, treatment, and rehabilitation of emotionally disturbed and mentally ill youngsters. This is accomplished through the Institute's intramural research program, grants-in-aid to the States, research grants and fellowships, training grants, the mental health project grant, and the hospital improvement project grant program, demonstrations and the professional and technical assistance provided through consultation, workshops, seminars and research utilization conferences.

Since its inception, the grants-in-aid program has been a significant factor in stimulating the development and expansion of community mental health and psychiatric services for children. The growth of clinic services for youngsters has been encouraged by these "seeding" moneys made available to local communities by the States from their grant-in-aid funds. A number of States also use portions of these funds for the training of personnel to work with emotionally disturbed children. For example, in California, the Peninsula Children's Center in Stanford is currently receiving $10,000 from the State's grant-in-aid funds for a day treatment program for mentally ill children.

The first group of proposals submitted by the States under a new grant program, the hospital improvement project grants, is currently being reviewed. As an indication of the priority the States attach to their level of need for treatment programs for emotionally disturbed youngsters, it is significant to note that 42 of the 188 projects submitted propose to focus on strengthening and improving inpatient treatment programs for children and adolescents. For many of these States, a hospital improvement project grant would enable them to initiate their first specialized inpatient program for mentally ill youngsters.

Since the inception of the mental health project grant program in 1958, about 150 separate project grants have been made which relate to prevention, identification, treatment, and rehabilitation of emotionally disturbed and mentally ill children and adolescents. Of these, 91 are currently active. Projects are focusing on a wide range of services, including, for example, training of nonprofessional personnel to work with youngsters in treatment and school settings; the organization of volunteer services to provide "mothering" for children institutionalized because of dependency; training of foster parents to handle emotionally disturbed youngsters; and structuring of school mental health programs as well as special programs for children from deprived neighborhoods.

To meet the special needs of children, mental health project grants have been awarded for a variety of research projects focusing on specific elements of the child's life.

In the area of delinquent behavior, for example, a number of grantees are concerned with finding more effective ways of treating adolescent delinquents.

Perhaps in many cases there is a more effective course than institutionalization. As a substitute, the California Youth Authority has been experimenting for 2 years with an intensive treatment-control program in the community. In this project, which is supported in part by the Institute, a treatment program is developed according to the delinquency pattern of each individual. Community agents work with caseloads of eight, using such techniques as individual, group, and family therapy; school, work, and activity programs; foster and group homes; surveillance and temporary detention. The cost of community treatment is reported to be higher than that of a field operation such as probation or parole but lower than that of the usual institutional program. Because the public recognizes that tight controls are exerted over the delinquents and that efforts are made to bring about permanent changes in them and their families, increasing acceptance of the project is reported. The effectiveness of community treatment is being compared with that of confinement.

Some investigators are concerned with maintaining the mental health of youngsters by enhancing the adequacy of their environment, including, for example, the classroom environment. In schoolchildren, healthy mental attitudes and effective learning have been found, by researchers working with Institute support, to be related to a classroom's social atmosphere. When the pattern of affection among class members is diffuse rather than narrow, so that almost every child is "most liked" by some other member, pupils tend to have more positive feelings toward themselves, perceive the school situation more favorably, and make fuller use of their potentials. These conclusions are reached after extensive observations and tests in four sixth grade classrooms.

For better mental health in the classroom and better academic progress, the investigators suggest that the teacher determine, by observation, aided perhaps by the sociometric techniques used in the study, how the group's affection is distributed. If a change is desirable, the teacher can use various techniques, such as a cooperative study group in which low and high status pupils work together, or a steering committee on which all pupils serve at some time during the year, thus achieving some status and self-esteem through being active contributors to classroom decisions. Also suggested are discussions of differences related to family background, race, abilities, and interests and programs directed toward a greater understanding of the causes of human behavior. If the teacher himself accepts each pupil as an individual, giving him the kind of support needed to expand his assets and help overcome his shortcomings, the investigators report, members of the class will tend to follow a similar pattern.

Investigating the effects of anxiety on the academic achievement of college students, a grantee found that anxious students in the middle ranges of ability got lower grades and showed a higher percentage of academic failures than nonanxious students of comparable ability. Students of low ability got poor grades whether anxious or not, but the nonanxious students were less likely to fail. Among the superior students, there was some indication that anxiety facilitated performance. Acting on these findings, the grantee and his associates offered group counseling to new students whose anxiety test scores indicated that the students would probably do less well than they could or might even fail. The findings: anxious freshmen who regularly attended group counseling sessions (a sixth of the total invited) showed a significantly greater improvement in their academic performance than anxious freshmen who were not counseled or who did not regularly attend counseling.

Other projects cover a variety of child mental health problems, for example, attempted suicides among adolescents; the need for family therapy for adolescent schizophrenics; the rehabilitation in sheltered workshops for older adolescents who have spent long periods of time as inpatients; and many others.

Technical assistance projects (TAP's) are workshops, seminars, or special conferences bringing together at the State or regional level, key personnel of State and local agencies and organizations to discuss and plan together for new and expanded mental health programs and services in priority program areas. The extent to which the States are concerned with programs and services for the mentally disturbed youngsters is evidenced by the fact that 10 percent of the TAP's held during the calendar year 1963 were specifically for this problem area. In addition, a significant portion of discussion time is devoted to the needs of emotionally disturbed youngsters at TAP meetings which are concerned with school mental health and with the cooperative activities of mental health and health and welfare agencies in developing and expanding community mental health programs.

Through contractual demonstration projects, the Institute is engaged in an effort to increase and make more efficient the dissemination of good practices to new settings and the translation of research findings into mental health program operations. A project completed in 1961 on school mental health casefinding in Volusia and Seminole Counties of Florida was a demonstration of a school mental health program in rural or semirural areas in which mental health trained personnel worked through the local health department with public health nurses and school personnel.

Two demonstrations have nationwide significance through their work and potential impact on mental health and guidance services in the schools. The Interprofessional Research Commission on Pupil Personnel Services demonstration which developed into a mental health project grant is a commission of education and six mental health professional organizations which will develop a program of collaborative research projects on school mental health services. It will also study the mental health needs of schoolchildren in rural and urban systems as well as the roles of the various disciplines in meeting these needs.

In the demonstration project to expand behavioral science foundations of guidance training at Columbia University, behavioral scientists will work with the educational guidance training faculties and education research personnel of 21 university schools of education to integrate behavioral science training into the preparation of guidance workers who will work in local schools. The research findings and the curricular designs will be published and distributed to the 1,200 teacher-training colleges in the Nation.

Final contract procedures are in process for a new demonstration which will have particular significance in the President's program of the attack on poverty. It is increasingly clear that the economy is faced with a chronic problem of fitting persons without jobs into careers where there are more jobs than people. At the present time and for the foreseeable future, it seems apparent that the greatest number of job opportunities will be in the area of "human service." It is also clear, from a number of studies, that the incidence of mental illness is higher among the lower socioeconomic, culturally deprived segment of society.

This new demonstration proposed to attempt to deal with both these problems. The Center for Youth and Community Studies at Howard University will set up a small exploratory demonstration program for 10 youths between the ages of 17 and 19 in economically and culturally deprived areas of Washington, D.C. This mental health social-action program for the selection, orientation, supervision, and utilization of community apprentices in such "human service" careers as child-care education and recreation will also serve as a technique of preventive intervention for adolescents.

RESEARCH UTILIZATION

One of the major functions of the Institute's Research Utilization Branch is that of intermediary between the research laboratory and field demonstrations and the agencies and groups responsible for developing and conducting mental health service programs. To implement this mandate into program development, the Branch is increasingly using research utilization conferences as a program resource. These meetings bring together experts, practitioners, and administrators to discuss and explore mental health program areas requiring special attention and thus stimulate the translation of research findings into operating programs.

In 1962, a panel meeting of investigation in followup studies of children in their own homes, adopted children, and studies of psychiatric referrals was held. The conference provided participants the opportunity to share experiences and to discuss research findings and methodology. It was the unanimous opinion of the group that this had been an invaluable experience in research utilization. Moreover, it was felt that the cross fertilization of ideas had been so stimulating that it would lead to further communication among members of the group.

The Research Utilization Branch has also jointly sponsored a conference with the Association for Supervision and Curriculum Development which was concerned with exploring new ideas for research and pilot projects to develop changes in school curriculums which are ego enhancing or ego building in their impact on children and adolescents. This is one of the chief concerns in the prevention of delinquency and other forms of social and individual maladjustments. Finding ways of building stress immunity or stress management techniques in children and adolescents using educational processes has important preventive implications.

In addition, within the Research Utilization Branch special staff consultants in school mental health, childhood mental illness, and child and family mental health concentrate on program activities in these areas. The staff of Clinical Facilities Section is also available for consultation to States and local communities on facilities and treatment programs for emotionally ill youngsters.

TRAINING

The total amount of funds awarded in fiscal year 1963 for support of mental health training for work with children was $7,350,000. It should be noted that, while this is not all specifically in the area of training for work with the emotionally disturbed child, much of this training would provide the professional skills for work with the emotionally disturbed youngsters.

Within this total, slightly more than $4 million could be considered specifically as training related to work with the emotionally disturbed child. Included are such areas as training in child psychiatry, training in psychiatric nursing in the specialty of child psychiatry, training in social work in juvenile delinquency and in corrections, and training in psychology in field training centers which are institutions for the care of the emotionally disturbed child.

In addition there are some specific pilot projects which provide training related to the emotionally disturbed child. For example, there is a clinical training program in a residential summer camp setting designed to provide intensive and varied experiences with emotionally disturbed children for graduate students in the fields of psychology, psychiatric nursing, psychiatric casework, and psychiatric group work.

At the University of Pittsburgh there is a program to train new groups of persons for working with institutionalized emotionally disturbed children. Two groups are those with master's degrees in child care work and child care worker technicians.

Another project is designed to provide multidisciplinary training for houseparents. Subprofessional personnel are being trained to serve as houseparents and home supervisors for residential child treatment institutions.

Three projects are designed specifically for training teachers of emotionally disturbed and socially malajusted children.

OVERVIEW

The activities related in this report are intended to describe, by example, the various programs in which the Institute is attempting to aid the emotionally disturbed child or adolescent. The intramural and extramural research programs, the demonstration projects, the aid to the States, and the training activities all are supported and encouraged to this end.

Work in the field of the disturbed child and adolescent shows most clearly the interaction between the innate characteristics of the individual and the social milieu. Each contributes to, as yet to an indeterminant degree, the difficulties of the youngsters. As our knowledge increases, our interventive techniques will improve. In time, with the dissemination of research findings, preventive measures will be developed. This is the ultimate goal, whether the immediate aim is to guide an acting out juvenile delinquent or bring autistic child closer to reality.

These immediate and long-range goals can be reached only through effective training of professional and subprofessional personnel—scientists, physicians, teachers, and laymen. For in this field of the emotionally disturbed child, as is true for the other vital fields in which NIMH is involved, the dedication of people is a prerequisite to success. It is fair to say, however, that it is impossible to predict the ramifications which advances in other fields, such as schizophrenia, alcoholism, psychopharmacology, etc., may have for this one. It is important then, that all facets of our research, training, and utilization programs be developed.

FELLOWSHIPS

Mr. Fogarty. You are supporting 1,004 fellowships in 1964 and are budgeting for 988 in 1965. Why are you cutting back here?

Dr. Felix. The reason is the same as that given by one of my predecessors, either Dr. Aldrich or Dr. Endicott. We, along with the rest of NIH, of course—it is an across-the-board proposition—are increasing the size of the stipends. This has become necessary because of the rising prices and all. This increase means more per unit. Therefore, we have had to cut back on the number in order to stay within the——

Mr. Fogarty. If you had more funds, would you be able to provide support for more fellowships in 1965—you have good people that need them?

Dr. Felix. If I found more funds available, yes, sir, I could support more. I am not asking for more at this time.

TRAINING GRANTS

Mr. Fogarty. You do have an increase in training grants from 1,722 this year to 1,946 in 1965.

Now, in our report last year, we encouraged you to do a little more on the general practitioner program and also on the new program of inservice training for nonprofessional personnel. Tell us how those programs are going and what your plans are for 1965.

GENERAL PRACTITIONER PROGRAM

Dr. Felix. Taking the general practitioner first, Mr. Chairman, we anticipate this year, 1964, we will award 588 trainee stipends in residency training in the general practitioner program; that is, both residency and the short-term training for the person who is going to remain in his own field and not go into psychiatry. That number is 588.

Mr. Fogarty. How does that compare with 1965?

Dr. Felix. May I put that in the record?

(The requested information follows:)

The general practitioner program of the National Institute of Mental Health, 1963 through 1965

[Amounts in thousands]

	1963		1964 estimate		1965 estimate	
	Number	Amount	Number	Amount	Number	Amount
Residency training	459	$5,940	588	$7,775	628	$8,600
Postgraduate education	2,900	1,114	3,000	1,225	3,100	1,400
Total		7,054		9,000		10,000

INSERVICE TRAINING

Mr. Fogarty. The other I asked about was the inservice training for nonprofessional personnel.

Dr. Felix. I spoke to this during my opening remarks, as you remember.

It is our anticipation from the volume and quality of the applications we have in the house at the present time, which will be acted on at this special council meeting, that we will award about 145 such grants this year. Hopefully, I cannot be sure, I would make no guarantee because these will be awarded on quality, but it is my hope, and it is only a hope, that we will be able to make at least one in every State.

We anticipate, with the funds requested for 1965, we will be able to award 105 more, making a total of 250.

Now, the benefits. These is no group of individuals in a hospital who come in contact so frequently for so long a period of time and so intimately with patients as attendants, house parents in the case of the retarded and the other children, and the so-called subprofessional people of this kind. The highest turnover rate in the hospital is in this group. They are essentially in many cases unskilled so far as this particular activity is concerned. I know hospitals in which the turnover rate is almost 100 percent a year in this category. You can imagine what this means to a person who is having enough difficulty adjusting to life as it is without having to adjust to new faces all the time.

We are hoping that, through this program, we will be able to bring more skill to these people and by bringing more skill to them, encourage them to take more seriously making a career in this activity rather than using it as a stopgap between this and some other job.

Mr. Fogarty. It might help them to get a raise, too.

Dr. Felix. Yes, sir. This is beyond my poor power to add or detract, of course. But if I am asked by any State, and I will say I have been by several, I would recommend strongly that they develop some kind of a career program, which I have envisaged, at least, for my own sake, on my background in Kansas—my town was a railroad town, and I thought of this as I have thought of brakemen and conductors, firemen, and engineers. I would recommend these people be brought in on what you might call an apprentice basis for 6 months, or whatever may be the proper time, at a modest salary. During this period of time they would get experience on the wards and elsewhere, they would also get the various kinds of inservice training necessary. At the end of this time they would be examined. They would either qualify and then have a tenured kind of position at some kind of salary, or they are out because they do not qualify. It would either be up or out.

If they qualify, there would be within-grade raises to permit a person to marry, raise a family, and have a decent life; and, after 2 or 3 years at the journeyman level, he would be able then to begin to participate in inservice training for the master's level. This is like they do it on the railroad, some of you may remember. After a certain length of time, the fireman can begin to get ready to take the examination for engineer. At such time as he is qualified, he takes the examination. He continues to work as a fireman until they need to run an extra section or during the summertime, during vacations, when people are taking their vacations, the top man on the seniority list moves over to the other side of the cab and functions as an engineer.

During that time he is paid as an engineer and eventually, through attrition, retirement, and so forth, he finally gets a regular run.

I would think of the same thing here, these people would qualify, there would be a pool of masters in every hospital. These would be people for the supervisory level. They would function during vacation periods, during peakloads. As he achieves more seniority, he would get more of this. Eventually, as attrition takes its toll, he would get a regular assignment. There would be probably several grades of supervisor up to, say, the supervisor of attendants for the entire hospital.

Now, I am told that this is going to cost money. Of course it is going to cost money. But I have tried to demonstrate here a little earlier that we are spending less money per hospitalization by improving our services to the point that these patients get better care and treatment, they get out sooner. The cost is more per diem.

Somebody asked me what I thought the supervisor of attendants for a hospital should cost. I said—I guess the person took a deep gasp, but I will say it again—I think such a person is entitled to at least $10,000 a year. Say that is the top for a supervisor, and you scale down from there. If you tell me $12,000 or $15,000, I will not gasp a bit. It is worth it. These are the people who come in contact with the patients every hour of every day, and they must have better training and orientation than they have now.

Again, I hope before we are through with this inservice training program, we will have such a grant, not to exceed $25,000 in every hospital for the mentally ill and every hospital for the mentally retarded in the country. If the Department and the Bureau of the Budget will permit, I will come back next year for an increase over what I am coming in now for in order to cover more of these hospitals, and I will do this each year if they will permit until I have covered all of them.

Mr. Fogarty. I am surprised you have so little in the budget for 1965.

Dr. Felix. Well, I believe this will cover——

Mr. Fogarty. That is just a drop in the bucket, as I look at it.

Dr. Felix. I can do a very good job with the amount of money here.

Mr. Fogarty. You would say that anyway, even if it was only half this much, I suppose. I just do not agree with you. I think you cannot do half the job you could if you had a little more money.

NATIONAL CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

We also recommended in our report that you continue the development of the National Clearinghouse for Mental Health Information. Tell us the current status of that project and your plans for the future.

Dr. Felix. Mr. Chairman, would it be agreeable to you if the Deputy Director, Dr. Yolles, speaks to this? This is directly under his supervision.

Mr. Fogarty. Go ahead, Doctor.

Dr. Yolles. The National Clearinghouse for Mental Health Information is still in the early stages of development. We have concentrated in large measure on a very careful, scientific, slow, steady development of this very, very needed facility in the mental health field. However, because our predictions, after a scientific study of the development of the clearinghouse, show it would take somewhere between 3 to 5 years for the necessary development of the clearinghouse, we felt that we must have available for dissemination to the field certain basic information now. Consequently, we have embarked at the same time on a series of pilot programs on contract with leading voluntary and scientific organizations in the country to supply us, or supply the clearinghouse with basic information in a number of fields.

For example, we are receiving information in the field of mental retardation, in the field of alcoholism, in the field of juvenile delinquency, in the field of children and youth, narcotic addiction, occupational psychiatry and a number of others. In addition to that, a pilot program which will give us information on mental health programs in six countries of Western Europe and the countries of Latin America has begun.

At the present time, there are about 40 persons working in the clearinghouse engaged in supervision of the acquisition of new material. Such material is coded, collated, analyzed, and stored in the clearinghouse and is made available for dissemination to a number of audiences, to the lay public, to professional organizations, to physicians in the field, to scientific organizations, to the researcher, et cetera, on request. During the next year, studies will be continued and intensified to determine the characteristics of the complex computer hardware needed for the clearinghouse.

Mr. Fogarty. Well, the committee agrees with you on the importance of this program. We just hope you have sufficient funds to keep the project going and get it in full operation as soon as practicable.

STATE PLANNING GRANTS

Now, there is a reduction of $4.2 million in State control grants. Is the planning that this amount was appropriated for in 1963 and 1964 going to be completed on schedule?

Dr. Felix. As far as we can determine at this date, yes, sir. I could almost give a categorical yes, except it is a little early for me to be able to do this and be sure that I can live up to my word. I am almost certain this is so. As I told you earlier, a number of States have already picked this up, 10 of them, as a matter of fact, in their own budgets after the 2 years had passed.

Mr. Fogarty. And three more——

Dr. FELIX. And three more are going to do it. And I would not be a bit surprised but what another dozen will do it before they are through.

Mr. FOGARTY. Do you think all States are doing a good job?

Dr. FELIX. Some are doing better jobs than others.

Mr. FOGARTY. What are some of the worst States?

Dr. FELIX. May I go off the record?

Mr. FOGARTY. Yes.

(Discussion off the record.)

Mr. FOGARTY. What do you think will be the beneficial results, overall, of this program?

Dr. FELIX. In planning?

Mr. FOGARTY. Yes.

Dr. FELIX. So far as I know, this is the first time that at least in the mental health field, and I would not be surprised but what it may be the first time in any major health field, that there has been a deliberate, organized, statewide planning effort conducted, based on the community resources, community need, and community facilities. It will make it possible for the States to assess where they are and where they should be in 5, 10, and 20 years. It will give them some idea what kind of personnel they should plan for. It will allow them to project what their budgets should be. And to plan to meet the needs.

Mr. FOGARTY. I think it is a good program.

TELESTIMULATOR

In your direct research activities, you mention the development of a remote telestimulator. You refer to it as "a potentially significant advance in techniques." What is this all about?

Dr. FELIX. Well, these are instruments which are really due to the development of the transistor kind of printed circuits. You can put receiving and sending equipment in a very small space. These are little radio receiving and sending sets which can be fastened onto an animal—we are using it with monkeys—and wires inserted into the appropriate parts of the brain. In the past when we have done these studies to find out what centers in the brain are the seat of certain kinds of emotional responses, we have had to keep the animal restrained. Now we do not.

You remember, Mr. Chairman, that in years past we talked about the monkeys who would stimulate themselves to the point where they would not even take water or food, the stimulation was so pleasant. With these instruments, we can put several moneys together in a room, and implant one of these sets in one of the monkeys and see how he responds in group situations, and how the group responds to him.

We had spoken earlier about family therapy, family situations. What is the influence of a disturbed child on the group? What is the influence of the group on the child?

We can now begin to separate these factors in animals, using monkeys or some other animals. You can begin to separate these things out so that you can control certain types of behavior and see what happens to the group. So this has very important implications for study of emotional disturbance in people and what the effect is upon a family, upon a schoolroom, things of that nature.

Mr. FOGARTY. I would appreciate it if you would supply additional information for the record.

Dr. FELIX. I can supply that.

(The information is as follows:)

RESEARCH ON TELEMETERING AND TELESTIMULATION

In the field of brain physiology, the research which is currently in progress in the telestimulation of the brain is one of the major breakthroughs in man's search to understand himself, his motives, and why he behaves as he does.

As in most instances of today's methods of communication, this study, this field of knowledge, is referred to by those men who are concerned in this quest by initials: ESB. These letters are the researchers' code for the electrical stimulation of the brain.

Neither the theory nor the practice is new. Man has been studying the brain for generations. Man has also been able to stimulate the brain electronically for at least 50 years, through what has become known as the "hard-wire technique." With hard wires men have been able to tune in on patients to find out how their hearts were beating, or how epileptic seizures were building up. But no one was sure that the results of charts and graphs so artificially obtained related significantly to the normal patterns of the man who was being tested.

Today, because of electronic competence in building anything from transistor radios-in-hand to telstar, we are standing on the threshold of discovery. Instead of the cumbersome, wired equipment which has allowed us to test some of the actions and reactions of the brain, we now have miniature senders and receivers. The "senders" are called "telemeters." They are tiny dime-sized sending sets which can be strapped to the wrist of an astronaut, for example, to tell the observers at the pick-up station what variations in heartbeat occur in the astronaut as he anticipates reentry into the atmosphere.

Men who want to know how the brain functions are now being given another tool—a miniature radio receiver-transmitter about the size of a commonly used pocket lighter, by which a radio frequency wave can be received and used to activate one or more parts of the brain. Through this device, man can learn what motivates and sets off basic patterns of behavior. This miniature device is a telestimulator.

This new equipment has not been used on human beings, but a series of experiments is in progress with lower animals—from rats to monkeys—which indicate that scientists will be able to achieve a knowledge of behavior with a high degree of precision until now unknown and unattainable.

Even with the limited knowledge and equipment available in the past, electronics has already produced devices and techniques which were extremely useful to behavioral scientists. Through electronics, men have been able not only to activate the brain, but also to measure the effects of different sorts of stimuli on the various parts of the nervous system, the glands and the muscles. Electroshock therapy has helped psychiatrists to treat certain mental disorders. The electroencephalograph (or EEG) makes it possible to record the progression of electrical activity in various parts of the brain which leads to an understanding of brain function in health and disease. These brain-wave patterns help doctors to locate and treat such things as brain tumors or other causes of organic malfunction.

But one of the most important new electronic developments is the extension of ESB to telestimulation. These new, miniature electronic senders and receivers owe their application, at least, to a technological breakthrough that began in Switzerland in 1932 with a neurophysiologist, Dr. Walter R. Hess, who received a Nobel Prize for his work. Dr. Hess managed to insert electrodes into the brain of the cat in such a way that specific parts of the brain could be activated to change the behavior of the animal. He was limited to use of the hard-wire technique.

With today's miniature equipment, however, the techniques developed by Dr. Hess now allow the subject of the demonstration to move freely without the entanglements and constrictions of the old-time hard wires, sockets, and other impediments.

Results of these new techniques are already a matter of scientific record. In university laboratories, for example, scientists have demonstrated that, in an established colony of monkeys, one monkey could learn to press a lever which stimulated the brain of another monkey and thus inhibit his aggressive behavior. In other words, electrical impulses initiated by outside stimuli caused the monkey to moderate or change his behavior.

Many stimuli operate invisibly on man's behavior, from sources which he cannot control, such as smog or other chemicals in his environment. Unlike these invisible stimuli, the equipment of ESB is neither invisible nor mysterious. The sending and receiving of these impulses are achieved through radiofrequencies like those used in all radio broadcasting. They are just as readily transmitted, detected, or jammed.

Their value in probing into the reasons for basic behavior is known in theory and in practice from experience with hard-wire techniques. But the newly developing equipment will make possible observations in more meaningful situations, thus contributing to man's knowledge of why animals behave as they do, and how that behavior can be changed.

We can assume, on the basis of research in progress today in ESB, that we will come to know what elements in the environment produce electrical or chemical changes in the brain, and cause one or more circuits to function differently than they do normally, resulting in changes and alterations in emotional patterns.

Obviously, this door into the knowledge of behavior will be of great significance in understanding and treating the mental illnesses.

Since the remote stimulation of the brain is already technically possible, our obligation is to utilize this new technique to find out as much as we can of the whys and wherefores of behavior, as quickly as possible, for the benefit of all men.

ST. ELIZABETHS PROJECT

Mr. Fogarty. How is your cooperative project with St. Elizabeths going?

Dr. Felix. It is going very well. It now has two aspects to it. I can expand on this for the record if you wish. We are continuing our studies in the basic area, studies of neurophysiology and pharmacology and psychology. But in addition to this, we have developed now an experimental hospital in this building, the William A. White Building. We have six inpatient wards. We are now following up on an outpatient basis the patients we have had in these wards. We are running a day care experimental program, and we are running also a home care service for technicians who have been on the wards over there.

I would like to point out here there is a unique opportunity at St. Elizabeths which, as far as I know, does not exist anywhere else in this country. This is a national hospital in the Nation's Capital, a hospital with a distinguished reputation going back a century. This hospital should be, in my opinion, a national demonstration of what is best in care and treatment at all levels. And it also should be a national resource for research.

This is what we are trying to develop through this cooperative program.

Mr. Fogarty. This committee is trying to make it one of the best.

Dr. Felix. Yes, sir.

Mr. Fogarty. We have given it everything it has asked for in recent years, and when the Bureau of the Budget did not allow a reasonable budget, we have increased it.

Dr. Felix. Yes, sir. I know this is true. I really wanted to be sure that the record showed that I think this is an important national resource which should not be overlooked.

RELATIONSHIP TO OTHER INSTITUTES AND AGENCIES

Mr. Fogarty. According to the justifications, you are doing some work on juvenile delinquency and on aging. In these fields, where is the dividing line between your Institute and the Institute of Child Health and Human Development; and, in the field of juvenile delinquency, the Department of Justice and Children's Bureau?

Dr. FELIX. As a rule of thumb, I have taken the preamble to the Mental Health Act and extrapolated from that.

The preamble of the Mental Health Act said:

> The purpose of the Act is to improve the mental health of the people of the United States.

I, therefore, assumed that since that was the reason the act was passed, which set up the Institute of Mental Health, authorized its establishment, that the charge to me through the act, as well as through the appropriations which have implemented it, has to be to improve the mental health of the people of the United States. Therefore, in any of these fields that you have mentioned, or in others in which part of the consideration is emotional and mental health or illness, promoting the one, preventing the other, I have felt that it was our responsibility, either alone or jointly with other activities in the Service, to prosecute this.

JUVENILE DELINQUENCY

In the field of juvenile delinquency, for instance, I do not feel that our primary concern is in the area of how institutions are run or in the judicial process for commitment of juveniles. I do feel that those aspects of delinquency which result from acting out or emotional reactions to broken homes, to working mothers, to gangs and the influence of gangs upon individuals in the gang, are appropriately our concern.

This is the reason why, for instance, in the $4 million-plus going into Mobilization for Youth in New York, the largest single contributor is the Institute of Mental Health—$1.9 million this year.

AGING

In the field of aging, I feel the same way, I am concerned with aspects of growing older which can contribute to maladjustment on the emotional level.

As I said a few moments ago, we supported a study in San Francisco on physical conditions which precipitated mental illness.

Now, what happened in older people? What happened was these people came to the hospital acutely mentally ill. This, then, becomes our concern.

In short, then, when there is an emotional component to the problem, to the degree that this is an emotional component, it is our responsibility, as I interpret it. And I feel that my colleagues, both in the Child Health Institute and in the Children's Bureau, and in other parts of the Department, so far as I know, agree with this.

MENTAL RETARDATION

Mr. FOGARTY. Now, in the area of mental retardation, are you in agreement with what Dr. Aldrich said earlier today about the division of responsibility between his institute and yours and the Children's Bureau?

Dr. FELIX. Yes, sir.

Mr. FOGARTY. Is there any overlapping or duplication that you know of in what you are doing and what they are doing?

Dr. Felix. If there is, it is intentional, because two people sometimes looking at the same thing, see it differently.

Mr. Fogarty. Give me an example where it is intentional.

Dr. Felix. Let us take the area of learning he mentioned this morning. I am concerned with learning theory and experiments in the field of learning for two reasons. I am concerned with this because psychotherapy, not drugs, but psychotherapy, is a relearning process. And in order to understand what I am doing, or to improve how I do it in psychotherapy, I must know learning theory and how to apply it. Therefore learning theory and how a child develops and learns as he develops becomes important to me, but from a different slant than to a person just interested in normal child development.

I am concerned with learning also because of the various inputs into a person's knowledge which can cause distortions of the concept of himself and his environment and will be conducive to emotional illness.

I have felt, and in talking with Dr. Aldrich and in talking with Dr. Shannon, it has been more or less understood that my areas of concern are as follows: In the area of retardation—you can apply this to children generally if you want; I am concerned with cultural deprivation, because this is an important aspect to emotional illness generally; and I can enlarge on this for the record if you want.

Mr. Fogarty. All right, do that.

(The additional information follows:)

The National Institute of Mental Health is responsible for program efforts in the mental health aspects of mental retardation, with responsibility for planning, stimulating, administering, and coordinating a program of research, training, technical assistance, and demonstrations, with special emphasis on (1) research, development of corrective or preventive approaches and special problems of manpower and professional training on the effects of cultural deprivation of children; (2) research, early diagnosis, prevention, and treatment problems in the field of mental illness that grow out of life experiences of the retarded; and (3) the area of learning, with primary interest devoted to learning in psychologically disordered states and with secondary interest in normative states, and with careful attention to the special problems of the retarded, in this connection.

ANTIPOVERTY DRIVE

Mr. Fogarty. What part do you play in this antipoverty drive?

Dr. Felix. We are concerned again because of the cultural deprivation aspects of the whole field of poverty.

One of my staff has been very closely associated with this and has been sitting in on conferences with the various people concerned. I do not know at this early date what our role will be. I would hesitate even to say anything because it is too early.

Mr. Fogarty. Yes. I understand the message has not been completed yet. I won't ask you to comment any further under the circumstances.

Dr. Felix. I am personally very committed, as a person, to doing all I can in this area.

Mr. Fogarty. I have taken a great deal of time; perhaps more than I should have.

Mr. Denton.

REDUCTION IN NUMBER MENTAL PATIENTS IN HOSPITALS

Mr. Denton. You made a projection for the record last year where you showed what the normal increase would have been in the number of patients in the hospital if this decline had not been brought about, and then you showed how the decline set in and the difference between the two. Do you have that chart brought up to date.

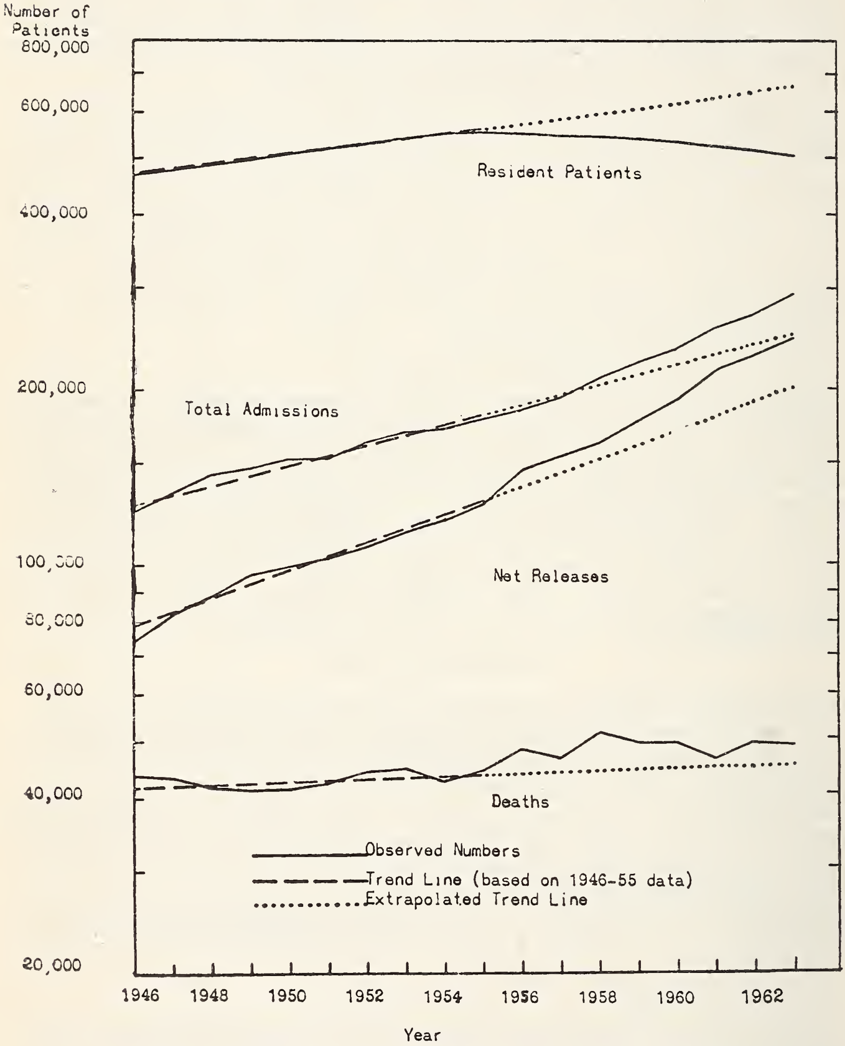
Dr. **Felix**. Yes, sir, I do.

Mr. **Denton**. Would you put that in the record?

Dr. **Felix**. I would be happy to.

(The chart referred to follows:)

NUMBER OF RESIDENT PATIENTS, TOTAL ADMISSIONS, NET RELEASES, AND DEATHS, AND EXTRAPOLATED TREND LINES (BASED ON THE YEARS 1946-1955), PUBLIC MENTAL HOSPITALS, UNITED STATES, 1946-1963



Source: Data collected in annual census of patients in mental institutions, National Institute of Mental Health.

DOLLAR SAVINGS

Mr. Denton. We have saved a very large sum of money because of this reduction, have we not?

Dr. Felix. It shows we have saved about $1 billion to date.

Mr. Denton. Yes, we have saved about $1 billion because of this program.

Dr. Felix. Yes.

Mr. Denton. That certainly justifies the expenditures we make in this whole program?

Dr. Felix. In my opinion, yes. The total amount of money appropriated for the National Institute of Mental Health since its establishment is in the neighorhood of $850 million.

Mr. Denton. You are not taking into account the amount of money the Government has saved in veterans' hospitals in this figure, either, are you?

Dr. Felix. No, sir.

Mr. Fogarty. Or pensions?

Dr. Felix. Or pensions.

USE OF DRUGS

Mr. Denton. That has been brought about to a large extent by these drugs that you use, transquilizer drugs and so forth?

Dr. Felix. This had made all the difference in the world. There have been other factors that played a part, but this has been the critical difference.

Mr. Denton. Those drugs have been developed, at least in part, by research grants given by the Institute of Mental Health?

Dr. Felix. That is right.

Mr. Denton. I do not mean to say they have done it alone, because the pharmaceutical industry has worked, too, and other people have, but they have been a very strong contributing factor.

Dr. Felix. That is correct. I might say and I think it should be said, that the reason that is so was because of the insistence of this committee that this be done.

Mr. Denton. Now, these drugs, do they have a habit-forming effect or not?

Dr. Felix. Certain ones do. One class they know of does. Others we do not think so. Some we are sure do not; some we still have to examine. One drug which apparently has some habit-forming effects is a drug known as meprobamate. You may know it under either one of two trade names, Equanil or Miltown. This drug has been found to have habit-forming effects if taken in large enough quantities over long enough periods of time.

This is not to say this is not a valuable drug and the drug of choice in certain conditions. But like some other substances, the doctor has to know what he is dealing with and how to use it. But it does have habit-forming effects.

Mr. Denton. Are there other drugs you can use that are not habit forming?

Dr. Felix. Yes, sir, there are. Whether or not they serve the purpose as well as meprobamate depends on the condition. This is part of what our whole evaluation program is doing.

I talked about certain drugs we now know have specific effects for specific conditions. Others we are still exploring. We have studied 190-some of these drugs, I think, so far; that is, we have looked at them to a greater or lesser extent.

Mr. Denton. Now, do these drugs cure or do they just ameliorate?

Dr. Felix. To the best of our knowledge, they do not cure, Mr. Denton. They keep the symptoms in abeyance.

I can give you an analogy, but please understand when I give you this that I am not saying they are the same thing; they are not at all. But just as insulin will allow a person who needs insulin, who has diabetes, to live a normal life with certain restrictions, similarly in many cases these drugs will allow a person who has been—or is, I guess you would say—mentally ill, to live a life less hampered by that illness.

Now, I say these are similar, but they are not, because insulin affects certain glands of the body; this does not. But on maintenance doses I reported earlier in regard to the study in New York City, Manhattan After-Care Clinic, they have been able to maintain people for 5 years on maintenance doses and the patients have been able to hold a job effectively.

Mr. Denton. Does the effect of it wear off?

Dr. Felix. So far as we can tell in the ones we have tested, chlorpromazine is the one most tested, it does not. One has to watch for cumulative effects. One has to watch for cumulative effects in the use of digitalis or sulfa;—well, not sulfa; of course, sulfa would not be given on a maintenance dose.

UNOBLIGATED RESERVES

Mr. Denton. Last year you were given $173,492,000. How much of that remains unobligated?

Dr. Felix. May I ask Mr. Van Staden, the executive officer, to answer?

Mr. Denton. Yes.

Mr. Van Staden. $2.6 million, Mr. Denton.

Mr. Denton. You have obligated practically all of it.

Mr. Van Staden. By the end of the year; yes, sir.

Dr. Felix. This is less than 1.5 percent of the appropriation.

Mr. Denton. How much is obligated right now?

Mr. Van Staden. As of January 31, $64 million, sir, in round figures.

Mr. Denton. I see. The balance will be obligated by the end of the year with the possible exception of the $2 million-plus figure which you gave?

Mr. Van Staden. Yes, sir. It is in reserve and under certain circumstances, it could be made available.

TRAINING GRANTS

Dr. Felix. You want to remember, one reason there is such a small amount at this point, our Training Committee meets once a year and our training money is awarded once a year only. And this is a large piece of money. That will be acted upon at the forthcoming Council meeting. So as of this time, there is a significantly less amount obligated than would be so if you were obligating proportionately each month of the year.

Mr. DENTON. These justifications show $73 million plus are for training grants. That is a rather large sum, but I believe that the difficulty you had in this field was that there were so few trained psychiatrists.

Dr. FELIX. Originally that was true; yes, sir.

Mr. DENTON. It was necessary to train them.

Dr. FELIX. Yes, sir.

Mr. DENTON. We have had that program for some years. Is it getting results?

Dr. FELIX. Yes, sir. You might be interested in some facts in this regard. In 1960, there were to the best of our ability to determine, 13,000 psychiatrists. In 1965, the projection, based on the end of 1963 figures, there will be somewhere between 17,800 and 18,400 psychiatrists. By 1970, the projection on the basis of what is now in the mill—that is, people in training, or who have declared an intention of going into graduate work in psychiatry, or are in medical school—there will be somewhere between 23,500 and 27,000 psychiatrists.

Mr. DENTON. I think I told you about when I visited a mental hospital and the doctor told me he had some 600 or 700 patients. He said all he could do was a lick or a promise. If he could work with the people, he could cause a great many to be cured.

Was that situation general over the country, and has there been any amelioration?

Dr. FELIX. Yes; it has. In a number of places, this is true.

You may recall, I think it was last year, I told you about Worcester State Hospital in Massachusetts in which they have been able to reduce their patient loads sufficiently so that a building which had been authorized for construction to accommodate the overflow was canceled, since they did not need to build it. Worcester State Hospital lowered its population by 40 percent and essentially maintained its staff so that they now have sufficiently smaller caseloads. The population is still going down.

Mr. DENTON. Do you think it is much cheaper to train psychiatrists than it is to have mental patients in hospitals?

Dr. FELIX. I think I can demonstrate that with a pencil and piece of paper. Yes. Yes, sir.

Mr. DENTON. Aside from the humane reasons.

Dr. FELIX. That is right. If one is concerned with dollars and cents, I think this can be shown to be true.

RESEARCH GRANTS

Mr. DENTON. Now, take your research grants. You have $76,495,000 for that. You will have that all obligated?

Dr. FELIX. Yes, sir.

Mr. DENTON. How are your projects rated, 1, 2, or 3?

Dr. FELIX. Yes, sir; they are all rated the same; what I mean is, all institutes use the same rating system.

Mr. DENTON. The research grants you have made projects that are in what category, 1, 2, and 3, or what? How far down have you gone?

Dr. FELIX. You mean have been made to date?

Mr. DENTON. In this year's appropriation.

Dr. FELIX. It may not all be in 1, 2, and 3. Let me tell you why. You would be the first to tell me that I should pay special attention to special areas, alcoholism, mental retardation, juvenile delinquency, drug addiction. In other words, to do this, I have taken a piece of this money and said, "This money shall go for these projects as long as there are any approved ones before we use it for something else."

Mr. Denton. I see.

Dr. Felix. Now, we will not take a No. 5, I will say, because this may get down too low, but we will take No. 4's, and even take them out of order in these particular areas, because this is—because I know of no way to stimulate a field as well as getting something going in the field, and somebody else gets an idea and we go from there.

FELLOWSHIPS

Mr. Denton. Comparatively speaking, you have a small sum in fellowships. How does that happen to be so? Lower than traineeships.

Dr. Felix. Fellowships is a special category of traineeship for training people in research. These are at three levels: There is the predoctoral level, which is those who are going to be Ph. D.'s, or some other doctorate degree, and they are going into neurology or psychology or something of that nature. There is the postdoctoral group where you have a Ph. D. in psychology who may want to do some work in physiology of the brain as it relates to mental processes, so he has to take some work in physiology. Then we have special grants. These are usually for people who are masters in their field who want to go someplace to do special work in a special place because the facilities are not otherwise available.

DRUG ADDICTION

Mr. Denton. Now, about narcotics. Did you ever hear of anybody being cured who had became a drug addict?

Dr. Felix. Yes, sir.

Mr. Denton. You have.

Dr. Felix. Yes, sir. Pardon the allusion to myself, but some of my patients have been cured, not many, but some.

Mr. Denton. Of course, I do not know many drug addicts, but all I have ever heard of, they might have it arrested for a while, but they always go back to it.

Dr. Felix. Mr. Denton, I had a man who came to the office not too long ago. My secretary said he wanted to see me, and I recognized him as a former patient. He said he wanted me to come down and see his wife. This man had had his home wrecked, his wife had left him. He got off of drugs, he came back. He was a professional man in one of the professions. We went downstairs, and his wife was sitting in a black Lincoln Continental that he had bought. He is better off than I am. And he is off of drugs. I treated him.

Mr. Denton. I know of a good many people who were alcoholic who have been cured and do not touch liquor.

Dr. Felix. That is right.

Mr. Denton. But of course, as I say, I do not know a great many drug addicts. But all I have ever heard of——

Dr. FELIX. Our results are not encouraging, if you look at the whole mass. When I get down in the dumps, get real blue about it, I can pick out some of these folks and remember they did not all go to pieces.

Mr. DENTON. I think that is all.

Mr. FOGARTY. Mr. Lesinski.

CHILDREN WITH MENTAL DISTURBANCES

Mr. LESINSKI. You mentioned the increase in mental disturbance of the age of 15 and down. What is the cause of that? Have you any idea?

Dr. FELIX. Well, it may be either one or two or three things. One, it may be actual increase; two, it may be that now that facilities have improved, people are more willing for their youngster to go to one of these facilities—because, remember what I said was that the number who are resident in these hospitals was increased. I do not know whether there are any more in the country, but there are more in these hospitals.

It may be that because we now have something to offer in the way of promise for treatment that these people are willing to come in. It may be that because of newer diagnostic techniques more of them are being identified as mentally ill where before they were thought to be brats of some kind and were treated accordingly, which did them no good.

I honestly do not know. That is the only honest answer I can give. Whether it is increasing or not, one could hypothesize, for instance, that in this time of strife and strain with all that is going on in our society and in the world, and how worried we are and what we may take home and communicate to our children, that there may be an increase. But I would be deceiving you if I said there was. I cannot prove it.

Mr. LESINSKI. Your remarks about the cuddly and uncuddly child—of course, I am not in that field and you do not look for things you would if in that field. I have never seen a child who was not cuddly, to be frank with you.

Dr. FELIX. Come out—not to my home; to my institute; I will show you some.

Now this does not mean they do not want to be cuddled at all, but a little bit is enough.

SIDE EFFECTS OF TRANQUILIZERS

Mr. LESINSKI. Yes. Now, in the various tranquilizers you use, you find some have side effects, not psychologically but physically.

Dr. FELIX. In some. As a matter of fact, there are some that have what we call side effects, in some of which we thought at first the side effects to be bad, now there is some suspicion one has to get the side effects before one gets maximum effects of the drug.

Mr. LESINSKI. Meaning how?

Dr. FELIX. Well, for instance, what we call Parkinson-like syndromes. You remember the shaking palsy? The fellow who has his hands going like this? Masklike face, shuffling gait? Some of the phenothiazine group, especially when pushed to the maximum tolerance level, will cause this palsy or shaking. It may be that you have to get to this level in order to get the patient over the hump before he will get better with certain of these drugs. But we are not sure. To date, we have always avoided, if we possibly could, side effects. As a result of this, certain of the drugs have been put aside as being not as good as others.

Now, someone comes along and says: "Maybe you are missing the best bet of all, you better find out."

Mr. LESINSKI. I have had experiences, but not with this type of drugs, with other drugs though, and I have found that there are side effects from them. I am on milk right now for that reason.

RESEARCH PROGRAM

You mention the research program for various institutions on a 10-year basis. Is that too long a continued basis?

Dr. FELIX. No, sir, Mr. Lesinksi; I do not think so. We carefully thought this thing through. I thought that 15 years would be too long, but I think 5 years would be too short.

Mr. LESINSKI. To me, 5 years seems enough to get an institution oriented to it.

Dr. FELIX. Ah, but we want to do more than that. We want to more than orient them. We want to find out how they can adapt it to their use. There may be 2 or 3 years of cut and try.

Mr. LESINSKI. I see.

Dr. FELIX. I am doing something in my institution and you want to take it over. All you know is it works for me. You are in Michigan, and I am in Maryland. You take it over and you find it kind of works, but there are a few bugs in it, so you modify it and you modify it again, and finally you find that apparently it works.

Now, you had better run that for 2 or 3 years and evaluate the results. In other words, you cannot just jump off the edge and say it works.

Mr. LESINSKI. You mentioned that you are not aiming for diversified studies. I commend you on that statement. I've argued with one of the other witnesses here in regard to this very thing. I always felt, and I know through life that everything has got some bearing upon something else. Therefore, with too diversified studies, you are not getting your maximum result for the effort, and I think you are quite correct in that.

I have no further questions, Mr. Chairman. Thank you.

Mr. FOGARTY. Thank you, Dr. Felix.

GRANTS FOR CONSTRUCTION OF COMMUNITY MENTAL HEALTH CENTERS

WITNESSES

DR. R. H. FELIX, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. STANLEY F. YOLLES, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH
GEORGE A. VAN STADEN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF MENTAL HEALTH
B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH
DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities: Grants for construction (costs—obligations) (object class 41)			35,000
Financing: New obligational authority (appropriation)			35,000

Mr. FOGARTY. We shall take up construction of community mental health centers now.

GENERAL STATEMENT

We shall put your statement in the record.

(Dr. Felix's statement follows:)

Mr. Chairman and members of the committee, the new Community Mental Health Centers Act forms the core of the new national program called for by President Kennedy, and is buttressed and supplemented by the other new and ongoing programs of the NIMH.

Looking forward to the implementation of this program, we at the Institute have formed the nucleus of a center's staff to undertake the planning required by the law. Our first task, in collaboration with the Division of Hospitals and Medical Facilities, is to draft the regulations required under section 203 of the act (title II, Public Law 88–164). These regulations will prescribe the general aims and proper operation of the program.

In addition, we are preparing guidelines for community groups interested in establishing their own mental health centers with Federal assistance under the act. The guidelines are being developed primarily for local physicians, psychiatrists, mental health boards, architects, and other professional groups who will be intimately involved in planning and constructing centers.

In an effort to anticipate questions which may be asked by such community planners, Institute staff members are now visiting a number of established mental health centers around the country. Their most important aim in visiting these centers, all with broad bases of experience, is to ascertain how best a community—urgan, suburban, or rural—can plan, build, and operate a comprehensive community mental health program and the facilities to house it.

Finally, we are actively seeking the participation and cooperation of professional and voluntary organizations in the area of mental health. For example, we are establishing formal liaison with the American Medical Association, the American Psychiatric Association, the National Association for Mental Health and the American Psychological Association, each of which now has staff members representing their organization's interests in the center's program.

In general, the act reflects the concept that many forms and degrees of mental illness can be prevented or ameliorated more effectively through community-oriented preventive, diagnostic, treatment, and rehabilitation services than through care in the traditional State mental hospital. The act is designed to stimulate State, local, and private action to provide comprehensive mental health services for all our citizens. It is based on the belief that it will be possible to reduce substantially, within a decade or two, the number of patients who receive only custodial care in an institution—or who are not under treatment at all—when they could be helped by the application of one or more of the modern methods of dealing with emotional disturbances and the mental illnesses.

The new legislation authorizes Congress to appropriate $150 million in Federal grants to States over the fiscal years 1965–67 for the construction of community mental health centers. Grants will cover from 33⅓ to 66⅔ percent of the cost of the project depending on the fiscal capacity of the State. Regulations establishing standards and procedures for the administration of this law will be issued in the near future by the Secretary of Health, Education, and Welfare.

States seeking to qualify for the use of these funds must submit, for the approval of the Secretary, plans that (1) designate a single State agency for the administration of the plan; (2) provide for a State advisory council; (3) set up a program for the construction of the centers; and (4) provide for a system of determining priorities among center projects. After the State plan has been approved, individual project applications may be submitted for approval through the designated State agency charged with administering the plan. At that time reasonable assurance must be given that adequate financial support will be available for the construction of the project and for its maintenance and operation when completed.

While the community mental health centers will care for severely ill patients as well as those less seriously ill, this does not necessarily mean that hospitalization in a specialized mental hospital will become either unnecessary or undesirable. As conceptualized, the centers recognize the need for close collaboration between community agencies and mental hospitals, and for a frame of reference in which the mental hospital is considered one facility and one resource, though not the sole facility or resource, in the whole chain of the community's armamentarium for dealing with mental and emotional illness.

In addition, the centers will implement several new concepts which point up the importance of active and interlocking community activity in order to promote mental health in the broadest possible sense. Some of these concepts include the growing awareness of the importance of social relationships in the etiology and treatment of mental illness; the increased interest in the study of the mental hospital as a social institution; the recognition of the importance of a therapeutic environment in the hospital and the community; the introduction of public health concepts in the plans for treating and rehabilitating the mentally ill; and the recognition of the special needs of the aged, the alcoholic, and the mentally retarded.

Taking into account the present state of mental health facilities in this country, and the importance of the considerations outlined above, a community mental health center will be a multiservice community facility designed to provide preventive services, early diagnosis, and treatment of mental illness on both an inpatient and outpatient basis, and to serve as a locus for the aftercare of discharged hospital patients. Thus it is generally agreed that the truly comprehensive community center should offer the following services:

A general diagnostic and evaluation service (precare);
An inpatient service; an outpatient service;
A day-care service; a night-care service;
An emergency service available around the clock;
Rehabilitation services;
Participation in foster home programs; and
Research and training.

Other essential services provided by the center will be consultative, educational, and information services to the public and to professional persons. Skilled staff will be available to help physicians, teachers, clergymen, police and probation officers, lawyers, and social agency personnel deal with the mental health problems of those they face in their day-to-day work.

Private physicians, including general practitioners, psychiatrists, and other medical specialists will participate directly in the Community Mental Health Center operation.

Since each community in which these centers is to be located is unique, each center will be unique. And it is expected that they will function under a variety of auspices: State, voluntary, municipal, private, within a group practice arrangement, or any combination of these.

Physically, it is expected that these centers will exist under different organizational arrangements, and may provide diversified services. For example, in one city, it may be decided that the Center would be based at a general hospital. Since most of the large general hospitals—those with more than 500 beds—already have psychiatric facilities, facilities for day care, night care, and outpatients could be added to fill out the comprehensive program.

In another community, it may be decided that the development of the Comprehensive Community Mental Health Center could be developed from an outpatient facility. Facilities for day care, night care, and inpatient services could be constructed with adequate office space for mental health staff to operate consultative and educational programs.

As one thinks of the array of services that will function as an integrated whole in the Community Mental Health Centers, he sees that continuity of care is possible, and that it would have enormous advantage to the patient. As his needs change, the patient in such a Center would move quickly to other appropriate services. Basically, he would be able to proceed from diagnosis to cure and rehabilitation, and back to treatment if the need arose.

Besides having available to him a full array of services, the patient could reap other benefits from community treatment:

> The patient's own family physician would be able to keep in contact with the patient and take part in the treatment program.
>
> The patient would be spared the pain of sudden separation from all that is familiar and the difficulty of readjusting to community life after institutionalization.
>
> Since many acutely ill mental patients can be successfully treated in the community in a matter of weeks, many patients would not have to give up their jobs during treatment.
>
> Family life would be less disrupted by illness; mothers would not be separated from their children for long periods of time.

While these centers will be primarily designed to serve the mental health needs of the community, they could also be available to provide assistance to those of the mentally retarded whose emotional and psychiatric problems cannot be met in other community resources.

A further benefit that could accrue to the community through the development of the centers would be that to an increasing degree, the costs of providing mental health care could be met through private financing in the form of individual fees for services, individual and group insurance, other third-party payments, and voluntary and private contributions.

The feasibility of this point, which was included in the President's message, is becoming increasingly evident. A recent Blue Cross study of the inhospital benefits received by more than a million subscribers under the health insurance plan for Federal employees showed that stays in the hospital for mental disorders were not much longer than for other illnesses. The average inhospital stay for mental disorders was 10 days, compared to 6.7 days for all conditions, and mental disorders accounted for only 3.1 percent of total hospital charges.

CONCLUSION

Mr. Chairman and gentlemen, appropriation by Congress this year of the $35 million authorized by the Community Mental Health Centers Act will make possible a major demonstration effort of the value of this new type of health facility. If, at the end of the 3-year period covered by the new legislation, the total amount of $150 million has been appropriated and some of the centers are operating, we should be well into the era of community-centered comprehensive mental health services.

The new era for which this legislation was designed holds many promises:

The promise of ending soon the neglect and isolation which has all too often been our pattern of dealing with many of the severely mentally ill;

The promise of returning mental health care to the mainstream of American medicine;

The promise of extending into many realms of our everyday life the productive use of the new insights into man's nature that the biological and behavioral sciences have developed in the 20th century;

And finally, the great promise that in our time we can lighten immeasurably, and for all time, the burden the mental illnesses have, in the past, placed upon mankind.

Mr. FOGARTY. Do you have a summary of the longer statement?

Dr. FELIX. I have a summary, and I have a longer statement. If it would please the committee, my summary is just a page; I will read this.

Mr. FOGARTY. All right.

Dr. FELIX. Mr. Chairman and members of the committee: The new Community Mental Health Centers Act, title II, Public Law 88–164, authorizes $150 million in grants to the States through 1967 for the construction of these centers. It is anticipated that about 230 centers will be established within the 3 years with the grants covering from 33⅓ percent to 66⅔ percent of the cost, depending upon the fiscal capacity of the State.

Regulations establishing standards and procedures for the administration of the act will be issued by the Secretary of Health, Education, and Welfare. States seeking to qualify for the use of these funds must submit State plans within which the projects will operate, and individual project applications which indicate adequate financial support for the centers.

The act is designed to stimulate State, local, and private action to provide comprehensive mental health services for all citizens. The research and progress in medical and social techniques has led to the firm belief that the number of patients who receive only custodial care in mental institutions can be substantially reduced, and I think that is a conservative statement. I think it can definitely be reduced more than just "substantially"; it can be cut in half.

The modern concept is that many forms and degrees of mental illness can be prevented or ameliorated effectively through preventive, diagnostic, treatment, and rehabilitation services within the community.

Mr. Chairman, the estimate for the first year of this program is $35 million, the full amount authorized.

Mr. FOGARTY. All right, Doctor, the request for this new program is $35 million, as you just said. Is this the full authorization?

ALLOCATION OF FUNDS

Dr. FELIX. Yes, sir, it is.

Mr. FOGARTY. How are these funds allocated?

Dr. FELIX. These funds will be allocated on the basis of a formula. I have had a committee of the staff working on this, and Dr. Yolles has chaired it.

Dr. YOLLES. The formula used in the allocation is similar to the one used in the Hill-Burton program. The three elements of the formula are: Population of the State, the financial need of the State, per capita income; and the need for comprehensive community mental health centers in that State.

Mr. FOGARTY. Is the allocation the same as the Hill-Burton?

Dr. YOLLES. The Federal percentages, the matching Federal percentages are the same.

Mr. Fogarty. So the matching requirements are the same as for Hill-Burton. Are applications approved by State agency or directly by the Public Health Service?

Dr. Felix. The State agency must draw up and submit a State plan for centers. This plan is approved by the Public Health Service. And part of the plan, some of the requirements, are the same as the Hill-Burton in this regard: The State must designate a single State agency, must have an advisory group, and so forth.

Mr. Fogarty. Just like the Hill-Burton program?

Dr. Felix. Yes.

Then, the plan for an individual project goes to the State. And after having been approved by the State and assigned a priority, and the priority under the law must take into account the comprehensiveness of the proposed center, then it comes to the Public Health Service for final review.

Now, I am extremely concerned that during the first few years of this program that this be done. I would point out that this program is a natural extension and natural growth of the mental health program as it has developed to date. The actual building is as important to the project as a shell is to a chick. It is what the activity is contained in, and it is important because it must be functional and there must be certain regulations met with regard to quality of material and labor and site and all of this. But this is an extension of the mental health program. This also is the dream coming true. And until I know that this is not going to misfire, I want to see these myself at least for the first few years. Then it will probably develop as the other programs have after that.

ELIGIBILITY FOR CONSTRUCTION FUNDS

Mr. Fogarty. Will you give us a little detail of what these centers will have to be, to be eligible to receive funds?

Dr. Felix. Do you want me to give it to you or put it in the record? I can put it in the record in detail.

Mr. Fogarty. Put the complete statement in the record.

Dr. Felix. All right, sir.

(The requested statement follows:)

Eligibility for Construction Funds Under Title II, Public Law 88–164

While some of the details involved in describing eligibility under this act will come out in the regulations (not yet issued), and thus cannot be fully discussed now, the principal criteria for eligibility determination are clearly evident:

1. An application for funds must come from a public or other nonprofit agency (or agencies) and must conform to the State plans for community mental health centers;

2. The State agency will assign a priority rating to an application based on the "relative need" of the area from which the application comes. Further considerations in determining priority are the comprehensiveness of the range of services offered by the facility, and the association of such facility with a general hospital.

3. If the facility to be constructed will not itself provide the essential elements of the full range of comprehensive services, then the services it does provide must be part of a program within that community which provides at least the essential elements of a comprehensive range of services. The essential elements of such a range of services are considered to be inpatient, outpatient,

partial hospitalization (day/night care) and community services (education and consultation).

4. Beyond the above listed, clearly programatic aspects of eligibility, there is one other factor of prime importance to consider: Is the applicant reasonably assured of the financial feasibility of the project, both for construction and operation?

5. Generally, of course, an applicant must conform to the regulations as promulgated by the Secretary of the Department of Health, Education, and Welfare, the provisions of the Davis-Bacon Act, and any other relevant provisions of local, State and Federal laws.

OPERATING EXPENSES

Mr. FOGARTY. How will the operating expenses be taken care of after they are built?

Dr. FELIX. Under the law as it was passed there must be reasonable assurance given by the applicant that the operating expenses will be met by one of several ways. It can be through some kind of governmental appropriation—I do not mean Federal; State, local, county, whatever—patient fees for services. I would hope, and President Kennedy, in his epic-making mental health message, indicated his desire, too, that as time goes on, an increasing amount of this will be met through third-party payments, health insurance of various kinds. I might say that it looks now as though this is even more promising than I told you last year. It can be through donations—a variety of ways.

There is no provision in the law as it was passed for any assistance through grants from the Federal Government.

DEMAND FOR FUNDS

Mr. FOGARTY. What indication do you have of the demand there will be for these funds?

Dr. FELIX. Dr. Yolles, would you give some indication as to this?

Dr. YOLLES. We cannot say exactly as yet what the demand will be.

Mr. FOGARTY. You must have a lot of inquiries from States.

Dr. YOLLES. That is exactly what I was going to say, sir. There have been many inquiries coming in from communities, from State-level organizations asking about it.

Mr. FOGARTY. Is there any question in your mind that the applications will amount to $35 million or more?

Dr. FELIX. Oh, it will be considerably over that, apparently. Already 35 States——

Mr. FOGARTY. I think this $35 million is a very conservative figure.

Dr. FELIX. Oh, yes.

Mr. FOGARTY. That is the authorization. There is not anything you can do about it.

Dr. FELIX. Oh, yes. I saw that the other day. From what I see now, our best estimate is that requests for Federal funds will come to $70-odd million in the first year.

Mr. FOGARTY. Twice as much?

Dr. FELIX. We have not even issued regulations yet. Dr. Graning of the Hill-Burton program and I have not had a chance to get together—the staffs have been working on it—but 35 States have designated their agency. For instance, Rhode Island has designated the "Department of Social Welfare" as the agency to operate this.

ADMINISTRATION OF THE PROGRAM

Mr. FOGARTY. The administration of this program seems to be split up within the Public Health Service. How much is budgeted and where, and why should it not all be in one place?

Dr. FELIX. The budget, it is a separate appropriation.

Mr. FOGARTY. For the administration?

Dr. FELIX. There is a separate appropriation assigned to the National Institute of Mental Health for administration; that is, we are the ones responsible for the expenditure of the funds.

The Hill-Burton people, however, are responsible for construction aspects and those things which have to do with what the Hill-Burton people are so experienced in doing.

I am charged by the Surgeon General with all aspects of the activities that relate to program.

Mr. FOGARTY. The funds for construction under the Mental Retardation Facilities and Mental Health Center Construction Act are split up among three appropriations.

You say it is all in the Hill-Burton program?

Dr. FELIX. I do not know.

Mr. FOGARTY. I guess Mr. Kelly would have to answer this, or Dr. Price.

Mr. KELLY. Well, in the case of mental retardation, Mr. Chairman, what we did was we put the community facilities in Dr. Graning's program of Hill-Burton and made him responsible for obtaining assistance as to the program content of the facilities from several different sources, each of which impinges upon this program, including child health——

Mr. FOGARTY. More than three?

Mr. KELLY. Yes, there are. But in the case of mental health, you have only the one organization that has a basic responsibility in connection with the quality content, working with the organization that has responsibility for the physical facilities. But in the case of mental retardation, we had to coordinate and bring to bear more than one organization that had a contribution to make as to what the content of these facilities should be. And this is why we handled the two in a different way.

Mr. FOGARTY. The Hill-Burton Act provided for various facilities, but you still had only one appropriation, is that not right?

Mr. KELLY. In the case of mental retardation, we are only appropriating the funds to one place; that is, the community facilities. The research facilities we are handling differently; we are handling those at the National Institutes of Health, the same as all of the research.

LANGUAGE ALLOWING TRANSFER OF FUNDS

Mr. FOGARTY. Please explain the proviso in the appropriation language.

Dr. FELIX. The what?

Mr. FOGARTY. The proviso in your appropriation language.

Dr. FELIX. Oh.

Mr. FOGARTY. Page 190, in the second line, starting with the word "provide"; the rest of that language, what does it mean?

Mr. Van Staden. That is the transfer authority. It leaves to the discretion of a State a determination as to which represents its greater need, mental retardation facilities or community mental health centers. It is interchangeable to the extent that a State certifies that it either has no approvable applications or there is a substantially greater need in one area or the other.

Mr. Kelly. Our problem was, Mr. Chairman, that if the appropriations for mental health facilities and mental retardation facilities were in the same appropriation, the act authorizes them to be interchanged under certain circumstances. But when we put them into two separate appropriations, we had to provide language which made possible this interchange.

Mr. Fogarty. This was not in the basic legislation.

Mr. Kelly. The basic legislation authorizes the interchange, but when you put them into two separate appropriations, we needed appropriation language that made it possible to carry out the intent of the basic statute.

Mr. Fogarty. Well, is this subject to a point of order?

Mr. Kelly. I think it is arguable whether it is, but a parliamentarian would have to rule on it. It is our rule that this is designed to carry out the basic intent of the legislation.

Mr. Fogarty. Do you think it is germane?

Mr. Kelly. I think it is.

Mr. Fogarty. I think you should put that provision of the law in the record so we will have the whole story.

Mr. Kelly. All right, sir, we will.

Dr. Felix. I cannot find it right off.

Mr. Fogarty. Supply it for the record.

(The requested material follows:)

Public Law 88–164, title II, section 202(c):

"(c) Upon the request of any State that a specified portion of its allotment under this title be added to the allotment of such State under part C of title I and upon (1) the simultaneous certification to the Secretary by the State agency designated as provided in the State plan approved under this title to the effect that it has afforded a reasonable opportunity to make applications for the portion so specified and there have been no approvable applications for such portion or (2) a showing satisfactory to the Secretary that the need for facilities for the mentally retarded in such State is substantially greater than for community mental health centers, the Secretary shall, subject to such limitations as he may by regulation prescribe, promptly adjust the allotments of such State in accordance with such request and shall notify such State agency and the State agency designated under the State plan approved under part C of title I, and thereafter the allotments as so adjusted shall be deemed the States' allotments for purposes of this title and part C of title I."

COMMENT

Title II of Public Law 88–164 authorizes appropriations in 1965 of $35 million for grants to States for the construction of community mental health centers. The funds are allocated to the States on the basis of population, the extent of the need for community mental health centers, and financial need.

Section 202(c) permits a State to request that a portion of its allotment under this title (mental health) be added to its allotment under part C of title I of the act (mental retardation) which authorizes appropriations in 1965 for $10 million for grants to States for the construction of facilities for the mentally retarded. The transfer authority in the act is conditioned upon the State certifying to the Secretary of Health, Education, and Welfare (1) that it has afforded a reasonable opportunity for the filing of applications for community mental health centers and has received no approvable applications; and (2) that the need for facilities for the mentally retarded is substantially greater than for community mental health centers.

Conversely, transfer authority is provided under part C of title I of Public Law 88–164 wherein a State may transfer its mental retardation funds to its mental health allotment—subject to the same type of conditions for transfer as indicated above.

Mr. FOGARTY. This is going to be a great step forward; is it not, Dr. Felix?

Dr. FELIX. Mr. Chairman, I find it a little difficult to be cold and dispassionate on this. But let me try to say it in just a word. This is the dream of my life coming true. Now, for that reason, it has a very deep meaning to me. I have given everything I have over all these years to see this happen. It is workable, it is reasonable, it is needed, it is desired.

The request for appropriations is carefully thought through and is money that will be used, I think, as fruitfully as any money appropriated by this Congress for any purpose whatsoever.

I can give it everything I have got. I cannot put it in strong enough words. We need this. We need it badly.

REDUCTION IN PROGRAM AS ORIGINALLY PROPOSED

Mr. FOGARTY. The original legislation, as introduced, was much higher than this; was it not? Was it not cut down in committee?

Dr. FELIX. Yes, sir; it was cut down and cut down.

Mr. FOGARTY. What was it originally?

Mr. VAN STADEN. The construction was a 5-year program—$330 million—and the fourth and fifth years were cut off—a reduction of $180 million. But the biggest item was between $400 and $500 million over a 10-year period for the initial staffing assistance of these centers, once constructed. The bulk of the cut related to the staffing provision.

Mr. KELLY. They restricted the length of the program.

Mr. FOGARTY. Yes, I remember that was really controversial on the floor when the bill was being considered. I thought it should have included staffing, and still think so.

Is there legislation before any committee up here——

Mr. VAN STADEN. Representative Ryan has introduced a bill to restore such authority which seems to be the same authority as was stricken from the original bill.

Mr. FOGARTY. But this $35 million for this year, was that in the original bill?

Mr. VAN STADEN. As I recall, that was the amount of the first year's construction.

Mr. KELLY. Yes.

Mr. FOGARTY. What about the total amount for construction?

Mr. KELLY. The total amount, you see, we had had as a 5-year program. But knocking off the last 2 years, means the program will stop at the end of 3 years so it was very severely restricted. However, if you visualize that, they will only evaluate how well we have done and then extend it, then they possibly did not reduce it.

Mr. FOGARTY. What is the thinking behind cutting a program like this that is so important and far reaching from 5 years to 3?

Mr. KELLY. Well, there seems to be an increasing tendency on the part of the legislative committees throughout all of the areas in which we operate and other parts of the Government, to reduce the number of years for which a program is authorized. In other words, so that the legislative committee will have an opportunity to examine what has occurred and determine whether it should be extended and under what terms and conditions.

Mr. FOGARTY. It not only cut down the period of years, but also cut down the amount that can be appropriated.

Dr. FELIX. This puts us in a bind in one way because each year's money is available for obligation for 2 years under the law. And if the program is to go on, we are going to have to come in in between 18 months and 2 years for renewal of legislation. Things will just begin to get underway and there will not be much to show. It puts us in a hard, difficult spot to demonstrate the worth of it.

Mr. KELLY. This is a very real problem. It is a problem that I think the executive and legislative branches somehow are going to have to face up to. Over and over again we are talking about extending legislation before we have had an opportunity to demonstrate what it can do, and legislative authorities are expiring before we appear before the Apropriations Committees, like Hill-Burton this year. There has been no extension yet, and yet beginning next July 1 there is no money unless the legislation is extended. It is going to become urgent at the end of the session, and then it has to be handled by a supplemental or budget amendment because it is not on a regular bill.

Mr. DENTON. The Hill-Burton program should have been renewed sooner than it is going to be.

Mr. KELLY. You have some basic problems associated with it, Mr. Denton.

Mr. FOGARTY. Is there anything else you want to say?

Thank you very much.

Dr. FELIX. Thank you, sir.

Mr. FOGARTY. Any questions?

Mr. DENTON. No, sir.

THURSDAY, FEBRUARY 27, 1964.

NATIONAL HEART INSTITUTE

WITNESSES

DR. RALPH E. KNUTTI, DIRECTOR, NATIONAL HEART INSTITUTE

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

R. H. HENSCHEL, EXECUTIVE OFFICER, NATIONAL HEART INSTITUTE

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH

DR. LUTHER L. TERRY, SURGEON GENERAL

LOYAL FISHER, DEPUTY DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
11 Personnel compensation:			
Permanent positions	4, 457	5, 141	5, 265
Positions other than permanent	119	110	110
Other personnel compensation	44	70	47
Total personnel compensation	4, 620	5, 321	5, 422
12 Personnel benefits	552	647	651
21 Travel and transportation of persons	250	306	309
22 Transportation of things	80	56	56
23 Rent, communications, and utilities	123	136	136
24 Printing and reproduction	15	66	66
25 Other services	1, 348	1, 880	2, 248
Payment of National Institutes of Health management fund	5, 935	6, 363	6, 616
26 Supplies and materials	912	1, 127	1, 131
31 Equipment	436	368	372
32 Lands and structures	159		
41 Grants, subsidies, and contributions	89, 909	99, 983	108, 972
Subtotal	104, 339	116, 253	125, 979
Deduct quarters and subsistence charges	21	22	22
Total obligations	104, 318	116, 231	125, 957

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	673	742	744
Full-time equivalent of other positions	23	21	21
Average number of all employees	635	687	686
Employees in permanent positions, end of year	652	703	705
Employees in other positions, end of year	46	29	29
Average GS grade	7. 1	7. 3	7. 3
Average GS salary	$6, 791	$7, 326	$7, 315

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	72,829	78,990	87,781
(*b*) Fellowships	4,747	6,207	6,207
(*c*) Training	12,333	14,786	14,984
Total, grants	89,909	99,983	108,972
2. Direct operations:			
(*a*) Research	10,662	11,248	11,545
(*b*) Collaborative studies	1,202	1,972	1,951
(*c*) Training activities	190	273	282
(*d*) Review and approval of grants	1,924	2,138	2,207
(*e*) Program direction	389	433	441
(*f*) Gerontology building	1	184	559
Total, direct operations	14,368	16,248	16,985
Total program costs, funded [1]	104,277	116,231	125,957
Change in selected resources [2]	41		
Total obligations	104,318	116,231	125,957
Financing:			
Comparative transfers to other accounts	16,279		
Unobligated balance brought forward	−1,000	−743	−559
Unobligated balance carried forward	743	559	
Unobligated balance lapsing	27,034	7,845	
New obligational authority	147,374	123,892	125,398
New obligational authority:			
Appropriation	147,398	132,404	125.398
Transferred to—			
"Operating expenses, Public Buildings Service," General Services Administration (76 Stat. 728)	−24		
"Salaries and expenses, Office of the Surgeon General" (42 U.S.C. 226)		−15	
"National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−4,981	
Appropriation (adjusted)	147,374	127,408	125,398

Mr. FOGARTY. The committee will come to order.

We shall now take the National Heart Institute.

GENERAL STATEMENT

Dr. Knutti, do you have a statement for the committee?

Dr. KNUTTI. Yes, sir, Mr. Chairman. I have already submitted a prepared statement.

(Dr. Knutti's prepared statement follows:)

Mr. Chairman and members of the committee, the past year has been the 15th since the establishment of the National Heart Institute. This decade and a half has brought substantial progress, and the past year has seen a continued strengthening of the attack on heart disease. Advances have been made both in the accretion of basic knowledge and in therapies which benefit hundreds of thousands of victims of heart disease.

Some of the year's accomplishments are spectacular, as in the instance of new gains in surgery for diseases of the heart and blood vessels. These range from saving the lives of tiny babies to aiding men and women of mature years who have suffered strokes. On the side of basic science, additions to knowledge are less dramatic, but will be meaningful in terms of human benefits in years to come. It is well to recall, for example, that today's almost incredible heart operations—in some of which more than one artificial valve has been placed in one human heart—would not be possible without recent fundamental knowledge from physiology, anaesthesiology, biochemistry, and so on. Yet, at the time many of these basic blocks of knowledge were reported, their value for surgery could not have been immediately foreseen or predicted.

As we move ahead next year, it can be said, however, that more and more clinical advances will be made and more and more cases of heart diseases will be amenable to treatments that will reduce suffering and add useful years to life. High blood pressure offers evidence for this view. In little more than the past 10 years, from research has evolved a whole array of useful drugs where there was none before. Life has been extended and much suffering relieved, and there has occurred a decrease of over 50 percent in the death rate from hypertension.

The current picture in coronary artery disease, from which come "heart attacks," is, of course, not as bright; and here lies the bulk of the heart disease problem. Here, too, however, there have been improvements in the therapy of damage—the treatment of existing disease, and there is hope that clinical advances, perhaps in the use of compounds now in experimental stages, will be of real value.

But it is from knowledge of the underlying causes, rather than improvements in the therapy of damage, that most of the great conquests of disease have come. Although we do not yet know fully the underlying causes of artery disease, a great deal has been learned in recent years, where formerly there was very little basic information and very few researchers engaged or interested in scientific investigation in the field of hardening of the arteries. Today, a base of knowledge has been built and is broadening more and more. Thousands of scientists of many fields and disciplines are now engaged in research involving hardening of the arteries, investigating clues ranging from the subcellular level to the level of studies of whole populations.

HEART DISEASE: SOME ENCOURAGING STATISTICS

An estimated 990,000 persons in the United States died of diseases of the cardiovascular system in 1963. Figures for specific causes of death are not yet available in 1963, but of the 957,437 deaths caused by cardiovascular diseases in 1962, 527,561 were accounted for by arteriosclerotic heart disease. Vascular lesions affecting the central nervous system accounted for 197,451 deaths, and 74,673 were caused by hypertensive disease, with or without heart involvement.

The total number of deaths from heart disease increased in 1963 over 1962, but the total population of the United States has also continued to increase in numbers and in age, which explains an increased total of heart disease deaths since there are more people and since diseases of the heart and blood vessels strike most heavily in the older age groups.

There are encouraging aspects to the statistical picture, however, when one examines the trend of death rates comparing the same age groups over the past decade. Arteriosclerotic heart disease, the most important cause of death, continued to have an increased rate between 1950–61. But, among women under 55, it dropped appreciably and, what is perhaps significant, the hitherto increasing death rate among white males seems to be leveling off. Although still increasing slightly at some ages, the arteriosclerotic heart disease death rate has actually begun to decrease (1 percent between 1957 and 1961) among men aged 55 to 64; and, in men of the ages 45 to 54 and 65 to 74, the rate is not increasing as rapidly as it was a few years ago.

The trend of death rates of hypertensive disease, vascular lesions affecting the central nervous system, and rheumatic heart disease is even more encouraging. All of these rates have decreased since 1950 among both men and women—a reduction to a rate one-half of that for comparable groups in 1950.

In general, death rates for all major cardiovascular-renal diseases as a group have decreased since 1950, with the greatest decrease among women of age groups from 45 through 74. Thus, there is cause for cautious optimism in the statistics of heart disease, and, although the bulk of the problem yet remains unsolved, progress is being made. If the rate of this progress can be accelerated, it is not too much to hope that the rate of increase of deaths from arteriosclerotic heart disease will not only cease, but also begin to show more and more definite trends of decrease.

NEW DEVELOPMENTS

At this stage in the march of progress against heart disease therefore the program of the National Heart Institute is directed toward developing and consolidating recent gains on basic and clinical fronts and probing new points of attack suggested by the findings of research.

Progress in program development has been made in a number of significant areas to take advantage of important trends and opportunities, among them the following:

In the 15 years of the National Heart Institute, its Directors have brought to you, year by year, brief accounts of annual progress and opportunities for research and its application to benefit people. Each year has added to the advances of the year before, but there has not been an overall evaluation, assessing not only progress of the years, but also all immediate and future opportunities for research, education, and the application of knowledge.

A new development for which intensive planning is now underway will be of interest to the committee and the Congress. This is the forthcoming Second National Conference on Cardiovascular Diseases, to be held in Washington late in January 1965. It will be sponsored by the American Heart Association, the Institute and the Heart Disease Control Branch of the Public Health Service. It will mark a decade and a half since the first national conference was held here under the same sponsorship, when both the Institute and the Heart Association were just getting underway. Much progress has been made since then, and the goal of this second conference will be to speed up the attack on heart disease and serve as a launching point for a great second-stage endeavor toward ultimate conquest.

In areas of substantive research opportunity which are available and which will increase the rate of progress, there are also developments of note.

One of the most promising and dramatic new developments is the propsect of an artificial replacement for the human heart. Through an intensified research effort, many believe, this is attainable within a few years, as are further great advances in organ replacements, already being successfully undertaken on a limited, experimental scale.

Thus, with the advice and cooperation of scientific groups and the National Advisory Heart Council, an artificial heart and organ replacement program is being planned. This will be of especial interest to the committee, which has noted progress in this field and recorded its encouragement of the planning and implementation of such an effort.

(A special report upon progress in this field and prosthetic hearts has been prepared and is available for the committee and the record if desired.)

Another new development of note lies in the field of cooperative studies of clot-dissolving agents.

Clarification of many of the body mechanisms involved in blood clot formation and dissolution has pointed toward new pathways for clinical treatment of patients suffering from thromboembolic complications of coronary heart disease. Thus far, however, there have been limited but promising clinical results. NHI grantees and other scientists have discovered and partially purified a series of substances which promote fibrinolytic activity. Greater knowledge is needed of these and of their modes of action, although some fibrinolytic agents have become available for clinical experimental use.

One of the most promising of these agents is urokinase, a protein from human urine, which poses fewer difficulties for widened pharmacologic studies and related limited clinical investigations and which offers hope for evolving material for sound treatment of coronary thromboses and arterial and venous clotting disorders.

A committee on thrombolytic agents, a counseling group to the National Advisory Heart Council, has been exploring the area. Through this group and the Council's work, a cooperative study of urokinase is being planned which may be carried out in a dozen or so collaborating institutions. The study is not being seen as a broad clinical investigation, but rather as one of basic pharmacological aspects with related clinical work involving perhaps 200 to 300 patients and of a carefully controlled, limited nature. From this, however, can evolve not only much needed fundamental knowledge of the nature and modes of action of urokinase, but also useful clinical knowledge that will lead further toward the safest and best clot-dissolving agents that can be developed.

PROGRESS IN HEART INSTITUTE RESEARCH

The research conducted intramurally by the National Heart Institute places major emphasis upon basic cardiovascular investigations. These studies seek new knowledge about the structure, function, and abnormalities of the cardiovascular system. Closely associated with these studies are those concerned with the application of fundamental knowledge to the diagnosis, prevention, and treatment of diseases of the heart and blood vessels. Some Heart Institute research in these two areas is described below.

Atherosclerosis.—Cholesterol has continued as the prime suspect in the development of atherosclerosis, with the amounts and kinds of fat consumed playing an important supporting role. However, eating fats is only the first link in an exceedingly complex chain of events in the development of atherosclerosis. The deposition of cholesterol and other fatty substances in the blood vessel wall is one of the last links in the chain. It is probable that the answer to the riddle posed by atherosclerosis is to be found somewhere between, in the complicated processes of fat metabolism.

Cholesterol: It has been amply demonstrated that saturated fats tend to raise serum cholesterol levels whereas polyunsaturated fats tend to reduce them; yet the mechanism or mechanisms whereby unsaturated fats work their magic have remained obscure. The manner in which the body handles different kinds of fat has been explored in a number of NHI studies in an attempt to define these mechanisms.

Fat absorbed from the digestive tract subsequently appears in the serum as chylomicrons. These tiny fat droplets, composed mainly of triglycerides (neutral fat), are carried to the liver and other tissues. Here the enzyme lipoprotein lipase breaks down chylomicron triglycerides to their component fatty acids, which are taken up by the tissues.

Studies on the fate of chylomicrons derived from corn oil (highly unsaturated) versus chylomicrons derived from cream (highly saturated) indicated that, while adipose tissue cleared both types with fine impartiality, the liver showed a decided preference for cream chylomicrons. This preference was subsequently verified by perfusing liver with a mixture of palmitic acid (saturated) and linoleic acid (polyunsaturated). The liver took up more palmitic acid from the perfusate.

Since the liver is the major source of serum cholesterol, triglycerides, and phospholipids, studies were carried out to determine the subsequent metabolic fate of infused fatty acids. The saturated fatty acid was preferred in the synthesis of triglycerides and cholesterol esters while the unsaturated fatty acid was preferred in the synthesis of phospholipids.

Fatty acids: Studies reported last year indicated that the mobilization of free fatty acids (FFA) from adipose tissue to meet the increased energy demands imposed by exercise or stress required an intact sympathetic nervous system and adrenal cortex. Thus, when animals were exposed to cold or forced to perform muscular exercise after their adrenal glands had been removed or after their sympathetic nervous system had been knocked out by drugs, their body temperature fell rapidly and they succumbed within a few hours.

The reason is that mobilization of depot lipid requires the activation of lipases—enzymes that break down adipose tissue triglycerides to FFA. The activation of these lipases requires the presence of norepinephrine from the sympathetic nervous system and hormones from the adrenal cortex—or so it seemed.

Current studies indicate that still another mechanism comes into play when the animal has been deprived of food for prolonged periods. As his tissue reserves of triglycerides fall, the animal keeps going by converting protein into energy sources. At this time his plasma FFA levels and adipose tissue lipase activity remain elevated. Neither the mobilization of FFA nor the activity of adipose tissue lipase in the near-starving animal can be blocked by knocking out the sympathetic nervous system with drugs.

Thus there appear to be at least two independent mechanisms for activating adipose tissue lipase, with only one requiring the mediation of the sympathetic nervous system.

Other studies indicate that adipose tissue contains a hormone-sensitive lipase that can be activated, not only by norepinephrine, but also by epinephrine, the pituitary hormone ACTH, and the pancreatic hormone glucagon. In earlier work, the degree of lipase activation observed when adipose tissue was treated with these hormones appeared to be so slight as to cast considerable doubt on the physiological importance of this lipase system. However, current studies have shown that, under suitable biochemical conditions, dramatic increases in lipase activity can be produced by very brief exposure of adipose tissue to any of these four hormones. Thus, this hormone-sensitive lipase system may play an important role in FFA mobilization during fasting or exercise.

Lipoproteins: These are large fat-protein molecular complexes that transport about 95 percent of the lipids in serum. A relative preponderance of low-density lipoproteins, which carry mainly cholesterol and triglycerides, is associated with increased susceptibility to atherosclerosis, whereas a robust high-density lipoprotein fraction appears to confer some measure of protection against the disease.

Continuing studies on Tangier disease, a rare disorder of lipid metabolism, indicate that plasma concentrations of high-density lipoproteins (HDL) may be determined by a single pair of allelic genes. In Tangier disease, both genes appear to be defective mutants, and so the individual has little or no plasma HDL. His serum cholesterol level is low, but large amounts of cholesterol esters are found in tonsils, lymph nodes, spleen, and other reticuloendothelial tissues. Studies among the kindred of patients with Tangier disease disclosed many individuals who were probably heterozygous: that is, only one of the two genes was a mutant. These individuals usually had very low plasma HDL values and elevated serum triglycerides, but showed no evidence of cholesterol ester accumulation in reticuloendothelial tissues.

These studies, together with studies on other syndromes characterized by low plasma HDL, indicate that high-density lipoproteins play an important role in the normal handling of cholesterol by the body. It also appears possible that a genetically determined deficiency of HDL may predispose the individual to excessive serum triglyceride levels, which appear to increase heart-disease risk.

Hypertension.—The major portion of NHI research on hypertension continues to be devoted to studies on the metabolism of amines. A number of amines seems to be involved in the mechanism by which the body regulates its blood pressure; and one of them, norepinephrine, appears to be the key to the action of most drugs currently used against hypertension.

In the sympathetic nervous system, norepinephrine is the chemical transmitter, or neurohormone, that conveys sympathetic messages between the nerve ending and its target organ. Sympathetic discharges can liberate norepinephrine to interact with receptors in the blood-vessel wall and cause constriction of that vessel; or it can be liberated in the heart to speed up heart rate, increase the vigor and efficiency of heart-muscle contraction, and increase cadiac output. All of these actions tend to increase blood pressure.

Many drugs currently used against hypertension reduce the flow of nerve traffic in the sympathetic nervous system by interfering with the storage, release, or metabolism of norepinephrine.

NHI studies have shown that alpha methyl dopa (Aldomet, Merck), a drug currently undergoing long-term clinical trials, reduces blood pressure by depleting norepinephrine stores at sympathetic nerve terminals. This compound is so similar in chemical structure to dopa, a precursor of norepinephrine, that it is processed by the enzymes that normally convert dopa to norepinephrine. Alpha methyl dopa, however, is converted to alpha-methyl dopamine and alpha-methyl norepinephrine. Either, or perhaps both, of these metabolites may be responsible for the subsequent large-scale release of norepinephrine that eventually drains the terminal stores of this amine and so prevents subsequent vasoconstrictive nerve messages from getting through to the receptors of the blood vessel wall.

NHI studies on norepinephrine synthesis indicate the cost of the norepinephrine stored in the heart and other sympathetically innervated tissues is produced locally from tyrosine, an amino acid derived from dietary protein. When tyrosine or other suitable precursors are infused into tissues that have been depleted of norepinephrine by drugs or other means, the uptake of precursors is rapid, the rate of norepinephrine synthesis is brisk, and the amine stores are rapidly repleted. However, in nondepleted tissues, norepinephrine synthesis from infused precursors is negligible. This suggests that norepinephrine synthesis may be adjusted to current tissue requirements by a feedback mechanism (wherein the accumulation of norepinephrine inhibits some earlier step in its production) or possibly by a humoral factor released by norepinephrine. Both possibilities are currently being investigated.

In recent years, intensive research has been done on the biochemical aspects of neurohormones at nerve endings. Although extremely valuable, the data gained from these studies had failed to provide any clear-cut picture of how nerve endings work. However, gradually emerging from studies done at NHI and elsewhere is a workable hypothesis concerning the structure and functions of nerve endings in the sympathetic nervous system.

According to this hypothesis, norepinephrine is present in organized structures in which the synthesis, storage, release, and metabolism of this amine are integrated processes. The expression “neurochemical transducer” has been coined to describe these structures because they translate an electrical nerve impulse into a quantity of free norepinephrine, which, in turn, acts on receptors of target organs to produce chemical or mechanical energy.

In the neurochemical transducer, norepinephrine synthesis goes on continuously. The norepinephrine is stored in two compartments or pools. The mobile pool consists of free norepinephrine which is immediately available on demand to handle sympathetic nerve traffic. This pool is replenished as necessary from the reserve pool in which norepinephrine is chemically bound and cannot be immediately released by nerve impulses.

The free norepinephrine in the mobile pool is surrounded by a fatty membrane. High concentrations of the free amine are maintained by an active transport mechanism, which impedes the escape of norepinephrine through the membrane by passive diffusion. Lurking outside the membrane is monoamine oxidase, an enzyme that quickly destroys any norepinephrine that manages to escape.

Sympathetic nerve impulses release norepinephrine by counteracting the active transport mechanism in that portion of the membrane facing the receptor. Thus a quantity of norepinephrine is allowed to diffuse through the membrane to transmit the nerve message to the target organ. After this norepinephrine has done its duty, most of it is promptly pumped back into the mobile pool by the active transport mechanism for future use. This thrifty use of norepinephrine, together with continuous norepinephrine synthesis, insures that the norepinephrine stores of the transducer will never become depleted under normal circumstances.

The neurochemical transducer hypothesis provides plausible explanations for the actions of many hypotensive agents. For example, reserpine and alpha methyl dopa deplete the amine stores of sympathetic terminals by knocking out the active transport mechanism of the transducer. Norepinephrine is thus allowed to diffuse freely out of the relative safety of the storage site, whereupon it is promptly destroyed by monoamine oxidase. Meanwhile, too little norepinephrine remains behind to handle the flow of sympathetic nerve traffic.

Surgery.—Primary pulmonary hypertension is characterized by constriction of blood vessels in the lungs. The resultant resistance to pulmonary bloodflow raises the pressure in those chambers of the heart (right atrium and ventricle) that drive the pulmonary circulation. The disease, whose cause is unknown, usually leads to death from congestive right-heart failure in 2 to 10 years.

NHI surgeons noted that patients with Eisenmenger's syndrome—in which pulmonary hypertension is coupled with a septal defect—generally fared better than did patients with primary pulmonary hypertension. Apparently, the septal defect protected against heart failure by acting as a safety valve. During periods of stress or exercise, blood could be diverted through the defect into the left side of the heart, thereby relieving some of the pressure on the congested right ventricle. The surgeons reasoned that the deliberate surgical creation of a septal defect might similarly benefit patients with primary pulmonary hypertension.

The results of animal studies have borne out this assumption. The surgically created shunt did prevent heart failure in animals with experimental pulmonary hypertension; and the surgeons feel that the operation might be equally effective in patients suffering from the disease.

PROGRESS IN GRANT-SUPPORTED RESEARCH

During 1963 the National Heart Institute's outlay for research grants totaled more than $77 million. This money was used to support over 2,200 cardiovascular research projects at universities and hospitals all over this country and numerous studies in foreign countries. The scope and diversity of these projects—which range from studies on large human populations down to studies on individual components of cells—reflect the magnitude and complexity of the problems posed by the cardiovascular diseases. Findings obtained from these studies resulted in the publication of over 3,500 scientific papers and abstracts. The following summaries represent only a small sampling of this impressive body of scientific literature.

Coronary heart disease.—Although much has been said about the possible contribution of high-tension living to the development of coronary heart disease (CHD), relatively few studies have dealt with this complex subject. However, early returns from a study of 3,524 men aged 30 to 59 indicate that behavioral patterns may be a valuable indicator of susceptibility to CHD. In this study a behavioral pattern characterized by aggressiveness, excessive competitive drive, chronic immersion in deadlines, and other "high pressure" traits appeared to be a better indicator of coronary proneness than did serum lipid patterns. Initial followup revealed that CHD had developed since first examination in 56 subjects. Forty-seven of these had been classified as coronary-prone on the basis of personality traits; 26 had been so classified on the basis of serum lipoprotein patterns. When compared with the remainder of the study population, these 56 exhibited slightly higher serum cholesterols, a higher incidence of hypertension, but no significant differences in physique, diet, exercise, smoking habits, or familial CHD. The scientists feel that these findings provide the first valid confirmation for a causal role of personality-behavioral patterns in CHD.

The strong association between elevated serum levels of certain fatty substances, notably cholesterol, and increased susceptibility to atherosclerosis has spurred the search for safe and effective means of bringing high serum cholesterols down to "normal" levels. An enzyme preparation called hepatocatalase, obtained from beef liver, has been found to inhibit cholesterol synthesis by the body and to reduce serum cholesterol levels in laboratory animals and in humans receiving it by muscular injection. NHI grantees report that the inhibition of cholesterol synthesis by the preparation does not result from the enzyme hepatocatalase, but rather from a peptide also present in the preparation. The scientists have succeeded in isolating the active inhibitor, a peptide of relatively low molecular weight. This suggests that, when its structure has been worked out, it may be possible to synthesize the compound. It also indicates that the compound is unlikely to produce anaphylactic or immunological reactions in the body (although no evidence of toxicity has been observed with the enzyme preparation either).

The clots or atherosclerotic deposits obstructing bloodflow through the coronary arteries are frequently confined to short segments of the involved vessels. However, surgery to remove or bypass these obstructions has heretofore been risky and likely to fail. The problem stems from the small diameter of the coronary arteries and from their tendency to constrict at incision sites and frequently to become further occluded by blood clots. The prospects of success in surgery on the coronary arteries have become brighter with the development of better methods for pinpointing obstructions and improved techniques for small-vessel surgery. NHI grantees report that, in experimental surgery using very fine sutures, miniaturized surgical instruments, and a dissecting microscope, they have achieved a high percentage of excellent results in coronary arteries as small as one-eighth inch in diameter. Procedures attempted included blood vessel splices, insertion of patch grafts, replacement of blood vessel segments, and others. Postoperative thromboses were rare, and most vessels remained patent. Highest failure rates resulted from closing incisions in the arterial wall by stitching the wound edges. The patch graft technique, in which the wound edges are sewn to an inserted elliptical patch of Teflon or Dacron rather than to each other, proved greatly superior in preventing subsequent arterial occlusion.

Hypertension.—Hypertension frequently results from clots or atherosclerotic deposits obstructing bloodflow to the kidney. The kidney reacts by releasing renin, which catalyzes the formation of angiotensin, a powerful blood vessel constrictor. NHI grantees report that, in addition to its direct vasoconstrictor action, angiotensin also intensifies the blood vessel response to drugs or to sympathetic nerve stimuli that trigger the release of norepinephrine at sympathetic nerve terminals. Sympathetic stimuli raise blood pressure by releasing norepinephrine to interact with receptors in the blood vessel wall. Angiotensin enhances this response, either by sensitizing the receptors to norepinephrine or by causing the release of larger amounts of norepinephrine by sympathetic nerve impulses. The scientists feel that this indirect action of angiotensin may be an important factor in renal hypertension.

Angiotensin is also the direct stimulus for the release of aldosterone, a hormone from the adrenal cortex that promotes salt and water retention by the kidneys. Aldosterone secretion is often abnormally high in many disease states, including congestive heart failure and malignant hypertension. Yet blood pressure remains normal in many instances in which aldosterone secretion (and hence angiotensin production) is elevated. Studies by NHI grantees provide a possible explanation for such instances. The studies indicate that aldosterone can inhibit the vasoconstrictor response to angiotensin. This represents a feedback mechanism of sorts, wherein aldosterone blocks one of the effects of the substance that regulates its release.

Congestive heart failure.—Counterpulsation is an assisted-circulation technique that has proved valuable during circulatory crises such as heart attacks or heart failure. By reducing the workload of the heart while maintaining or increasing its blood supply, counterpulsation helps to tide the heart over until it is once again able to meet its circulatory obligations. In this technique, blood is withdrawn from the femoral artery as the ventricle contracts. This reduces the pressure against which the ventricle must pump blood and thus decreases heart work. During diastole, as the ventricle relaxes, the blood is returned to the circulation, thus increasing coronary perfusion pressure.

Counterpulsation appears to be a safe procedure, even when applied over extended periods. However, the search has continued for effective techniques that would not require cannulating an artery or the cyclic withdrawal and instillation of blood, with their attendant dangers of clots or damage to blood cells. A recent grantee study indicates that support can be supplied to a failing circulation without entering the bloodstream by using a leg and abdominal pressure suit to apply pressure pulses synchronized with the cardiac cycle. By this technique, the arterial tree of the legs was made to function as a "booster pump." Like counterpulsation this technique raised diastolic pressure higher than systolic pressure, and it increased heart output by 33 percent when tested in animals.

Dopamine, the chemical precursor of norepinephrine, may be clinically useful for improving circulatory dynamics and clearing edema in congestive heart failure. NHI grantees have used dopamine in the treatment of a number of patients, some of whom had failed to respond to conventional modes of treatment. During the infusion period, dopamine increased blood pressure moderately in most patients and greatly augmented urinary sodium excretion, apparently by increasing renal bloodflow. The compound also effectively increased sodium excretion in doses that did not raise blood pressure or cause chest pain in patients with severe angina pectoris.

Patients under treatment for congestive heart failure appear to be especially susceptible to blood vessel occlusion and other complications stemming from blood clots. NHI grantees report that this clotting tendency might be due in part to increased blood viscosity during diuretic therapy. They found that, as patients became free of edema, their blood viscosity increased sharply, peak increases averaging 40 percent. This was associated with a rise in the concentration of red blood cells and of fibrinogen. Fibrinogen is the precursor of fibrin, the structural substance of blood clots. Earlier work by these scientists had shown that blood viscosity is importantly affected by the fibrinogen concentration. The grantees suggest that diuretics be used with caution in congestive failure so as to avoid too abrupt changes in plasma volume and resulting hemoconcentration. They also suggest that anticoagulants or other measures to prevent clotting be instituted during diuretic therapy.

Surgery.—Artificial pacemakers have been used with considerable clinical success to maintain heartbeat when elements of the specialized conduction system (which originates and transmits the electrical impulses causing heart muscle contraction) have been damaged by disease or operative injury. Conventional pacemakers are set to drive the heart at a predetermined rate. However, recently developed by NHI grantees is a pacemaker that can adjust heart rate to conform with shifting circulatory demands imposed by exercise or other factors. The new pacemakers picks up electrical impulses from the sinoatrial node (the heart's natural pacemaker), amplifies them, and transmits them to the ventricles. The sinoatrial node is responsive to nerve and hormonal factors that normally regulate heart rate, and the artificial pacer sees to it that the ventricles receive the instructions. The pacemaker also contains a fixed pacer circuit that automatically assumes control of heartbeat if the sinoatrial node should fail. Powered by long-life batteries and totally implantable, the new pacemaker has been successfully installed in a number of patients.

NHI grantees have achieved gratifying results against congenital heart defects producing severe cyanosis by performing corrective or palliative surgery in a compression chamber containing pure oxygen at a pressure of 3 to 3.5 atmospheres. At these pressures, enough oxygen is forced into physiological solution to increase the oxygen content of red blood cells by 50 to 100 percent. The increased supply of oxygen enabled severely cyanotic infants with tetralogy of Fallot, transposition of the great vessels, pulmonic or aortic stenosis, and other defects to undergo palliative or corrective surgical procedures that could not have been tolerated otherwise. Animal studies by other grantees indicate that high-pressure oxygen therapy is also beneficial against massive pulmonary embolism and hemorrhagic shock, and that it protects vital cerebral and circulatory functions when the blood supply to the brain is compromised by arterial blockade.

Their excellent operative results with single valve replacement has encouraged a team of NHI grant-supported investigators to attempt replacement of more than one disabled valve during a single operation. Of eight patients, five are alive and well. In one patient, three diseased valves were replaced; in two, the aortic and mitral valves were replaced; and in two others, replacement of one valve was coupled with surgical repair of another. The patients were on the heart-lung machine from 3 to 5 hours. During this prolonged period of heart-lung bypass, the heart was protected by perfusing the coronary arteries with cold blood; the kidneys were protected by adding mannitol, a diuretic, to the blood used to prime the heart-lung machine; and a high flow of blood was maintained to insure adequate tissue perfusion.

A sac type of artificial heart, implanted in the thoracic cavity of 22 dogs, has successfully maintained the circulation for periods up to 27 hours, NHI grantees report. To make insertion easier, the artificial heart consists of two separate pumps; one to drive the systemic circulation, the other to drive the pulmonary circulation. The ventricles of each pump consist of collapsible sacs located within rigid housing. They are driven by bursts of compressed air introduced into the rigid housing to compress the blood-filled sacs. Heart rate, vigor of contraction, and other factors affecting heart output are geared to venous return by a servomechanism. Thus, the output of the artificial heart can be adjusted automatically to conform with shifting circulatory conditions in a manner similar to that of the normal heart. (This and other types of artificial hearts are described in greater detail in a special report accompanying this statement.)

PROGRESS IN COLLABORATIVE STUDIES

The collaborative studies program provides a mechanism for extending Heart Institute research beyond the laboratory bench of the basic scientists and beyond the bedside of the patient to the broad population groups within which heart diseases are occurring.

Two reasons for emphasizing this area of research are: First, that research findings from the laboratory or from individual patient studies provide clues and hypotheses, but these must be proven true in the normal circumstances of life. The extension of research to population studies provides knowledge from which the general experience can be established in contrast to the variability possible for the individual. Second, since the ultimate proof of theories of disease causation must be obtained from observations on humans, the study of disease differences in large populations living under contrasting cultural, geographical, dietary and environmental circumstances provides the experiments of nature that the researcher himself could not possibly create.

Specific objectives of the collaborative studies program of the Heart Institute include:

(1) Conducting research in populations where "experiments of nature" have resulted in unusually high or unusually low rates of cardiovascular disease in order to identify the factor or factors contributing to relative susceptibility or immunity to these diseases.

(2) Experimentally modifying diet, serum cholesterol, or other factors believed to increase the risk of cardiovascular disease to determine whether such changes can materially reduce heart disease risk.

(3) Providing technical assistance and advice to investigators engaged in epidemiological studies to make their research more effective and their data capable of comparison with that from other carefully done studies.

(4) Conducting biometrics research and providing assistance and consultation on the design of experiments and on data analysis to NHI scientists and grantees.

These activities are carried out through direct operations, as in the Framingham study, through contracts, and through collaboration with grantees and other scientists here and abroad.

You have heard in previous years of the Framingham study which has now clearly identified several risk factors relating to coronary disease. Such factors as elevated serum cholesterol, high blood pressure, overweight, certain electrocardiographic abnormalities, and cigarette smoking are definitely associated with increased risk of coronary heart disease. Combinations of these factors may give as much as a tenfold increase in risk in comparison with persons with normal or low values.

The risks of developing cerebral vascular disease or stroke appear to be different. Cholesterol level of the serum does not seem to be important whereas elevated blood pressure and overweight are risk factors. Fewer than 50 cases of celebral vascular disease have thus far occurred in the more than 5,000 persons being followed in the Framingham program. However, the original group is now 13 years older so that cases needed for comparative study will be occurring more frequently.

The Framingham study has revealed important factors that increase the risk of coronary disease in an "average" New England community. This "average" community does not provide the variety of contrasting patterns of diet, physical activity, or cultural patterns needed to test other hypotheses. To find such populations we have begun studies in Israel, in Yugoslavia, in Puerto Rico, and are planning a study of persons of Japanese ancestry now living in Hawaii.

Another collaborative project is seeking factors that might be responsible for the striking differences between Britain and the United States in mortality rates from heart disease and from chronic respiratory diseases such as bronchitis and emphysema. Mortality from heart disease among British males is considerably lower than that among American males, but mortality from chronic respiratory diseases is much higher. The rapid increase in mortality from chronic respiratory diseases in the United States (it has more than doubled during the past decade) makes it particularly important to learn more about factors that might be responsible for this increase.

Health information is presently being collected from about 25,000 adults of British ancestry now living in the United States for comparison with similar data from their American contemporaries and with data obtained from siblings still living in Britain. A similar group of about 14,000 adults of Norwegian ancestry and brothers and sisters living in Norway will serve as the control group, since Norway has low mortality rates from both heart and respiratory diseases.

These experiments of nature—similarities as well as differing patterns of heart disease among the world's people—are irreplaceable opportunities for learning of factors that protect against heart disease or accelerate its development. We hope that the increased interest in epidemiology and geographical disease studies will continue to take advantage of these research opportunities before they disappear.

DIGEST OF RESEARCH ACCOMPLISHMENTS

Among the hundreds of research findings reported, as a result of research conducted during the past year by NHI scientists and grantees, were the results of studies showing—

That the different manner in which saturated and unsaturated fats are handled by the liver may be an important factor in their effects on serum cholesterol levels.

That two distinct lipase-activating mechanisms may play important roles in the mobilization of free fatty acids in response to fasting, exercise, or stress.

That a genetically determined deficiency of high-density lipoproteins may cause abnormalities in cholesterol or triglyceride metabolism.

How alpha methyl dopa reduces blood pressure in hypertension.

That most norepinephrine present in the heart and other sympathetically innervated tissues is synthesized locally, and that synthesis is probably geared to current tissue requirements by a feedback mechanism.

That dopamine-beta-oxidase inhibitors apparently hold little promise as potential therapeutic agents against hypertension.

That a recently developed hypothesis on the nature and function of sympathetic nerve terminals provides plausible explanations for the action of many blood-pressure drugs.

That "high-pressure" personality traits may be an important factor affecting susceptibility to heart disease.

That a peptide of low molecular weight is responsible for the cholesterol-lowering properties of an enzyme preparation called hepatocatalase.

That surgery on the coronary arteries is technically feasible with the use of microsurgery techniques.

That the ability of angiotensin to intensify the blood-pressure response to sympathetic stimuli may be an important factor in renal hypertension.

That aldosterone damps the blood-pressure response to angiotensin.

That counterpulsation provides valuable support to the heart during circulatory crises such as heart attacks or congestive heart failure.

That a failing circulation can be assisted by a pressure suit which makes the arterial tree of the legs function as a booster pump.

That dopamine infusions may be clinically useful for improving circulatory dynamics and for clearing edema in congestive heart failure.

That a new artificial pacemaker can adjust heart rate to conform with shifting circulatory demands imposed by exercise and other factors.

That surgery performed in a pressure chamber containing oxygen at 3 to 3½ atmospheres has achieved gratifying results against congenital defects causing severe cyanosis.

That improved life-support techniques during open-heart surgery make it possible to repair or replace more than one heart valve during a single operation.

That an implantable sac-type artificial heart has maintained the circulation of dogs for as long as 27 hours.

In conclusion, Mr. Chairman, the appropriation request for 1965 for the National Heart Institute is $125,398,000 as compared with the $116,047,000 available in fiscal year 1964. The increase for 1965 will provide for program activities in the following areas:

Research projects.—Continuation and supplementation of existing program, additional indirect costs on approved grants, and additional general research support grants.

Training.—One additional 4-year undergraduate school and increased costs of the average graduate training grant.

Review and approval of grants.—Support of additional clerical personnel to support an increased grant workload.

The request for 1965 is distributed among program activities as follows:

Grants:	
Research	$87, 781, 000
Fellowships	6, 207, 000
Training	14, 984, 000
Subtotal grants	108, 972, 000
Direct operations:	
Research	11, 545, 000
Collaborative studies	1, 951, 000
Training activities	282, 000
Review and approval of grants	2, 207, 000
Program direction	441, 000
Subtotal direct operations	16, 426, 000
Total 1965 appropriation request	125, 398, 000

Dr. Knutti. This statement contains a résumé of a few of the outstanding accomplishments in cardiovascular research in the past year. Before discussing any specific research findings, I would like, if I may, sir, to tell you about some of the activities of the past year in the selection and planning of some specific programs.

NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES

In the past year, as you know, the National Advisory Heart Council has played a leading role in giving the Institute advice as to substantive needs and opportunities in the cardiovascular field. More recently, two developments have been taking place which we feel are of the utmost importance in the planning activities. The first of these is the increased responsibility assumed by the Council; the other is the extensive plans for the Second National Conference on Cardiovascular Diseases, which is being planned for next January, that is January 1965, in Washington.

Mr. Fogarty. That is going to be quite a meeting. I have a letter from Dr. Andrus I just received a few days ago advising me of this meeting that is going to be held at the Sheraton Park, is it not?

Dr. Knutti. That is right.

Mr. Fogarty. January 25, 1965; is that right?

Dr. Knutti. Yes, sir. And I have some comments in more detail about this meeting I would like to discuss.

Mr. Fogarty. I wish you would, because I have been asked to make a speech there. They have sent me a newsletter I have not had a chance to read yet.

Dr. Knutti. I will be glad to.

PROGRAM PLANNING COMMITTEE

For the moment, however, to go back to the first of these; that is, the activities of the National Advisory Heart Council Program Planning Committee, this Committee is composed of a few of the Council members and, over the past 2 years, it has assumed a greater role, I believe, than it has in the past. They have devoted increasing amounts of their time to a study of the areas in cardiovascular disease which show promise for development for subsequent possible support.

One result of the activities of this Committee has been the formation of several groups of outstanding scientists to study and to make recommendations to the Institute concerning research in their areas of competence. Some of these groups have been assembled as ad hoc committees. A few of them have been formed as permanent committees which have been giving continuing study and surveillance of their specific problem areas, along with advice, to the Institute.

CLOT-DISSOLVING AGENTS

For example, we currently have a permanent committee for the study of thrombolytic agents. The activities of this committee have resulted in a series of recommendations out of which has developed a program for the production of urokinase. Urokinase is an enzyme, found in human urine, which shows signs of great promise in dissolving intravascular blood clots. We are presently processing some contracts for the development of this material and the production of a sufficient amount of it to supply to some investigators for clinical testing and evaluation.

The rationale which motivates this effort, is, of course, the possibility of dissolving recent blood clots in coronary or other vessels, such as cerebral vessels or in veins; dissolving these clots early enough to, hopefully, prevent death or serious destruction of heart muscle or brain tissue as a result of the occlusion of an artery by a clot. We feel this is a very important development.

I think if one reads the Soviet literature and takes it seriously, they may be ahead of us in this respect. At least they are testing a number of agents, not urokinase, which do dissolve clots.

I had the opportunity last fall, as a member of an exchange mission, to see some of the work that is going on there and, in this particular field, they seem to be moving somewhat faster than in some other fields important in cardiovascular disease.

Mr. Fogarty. How would you explain this field in layman's language? Are you talking about anticoagulants now or some other therapy?

Dr. KNUTTI. No, sir. I am talking about a substance which will dissolve a blood clot once it has been formed. In other words, in coronary thrombosis, the artery is occluded by a blood clot which is composed in the early stages of fibrin. Fibrin deposits and entraps blood cells and blood platelets, the formed elements of the blood. In other words, a blood clot forms.

First, at the very early stages of the formation of this clot, it is of a soft character. If such a clot is treated in a test tube with certain enzymes it is very susceptible to their action. These enzymes, called proteolytic, act upon the fibrin, which is of a protein nature, and dissolve it, thus destroying the clot.

Mr. FOGARTY. Well, suppose one of us has a coronary right now. What would be the next move then? What would you try?

Dr. KNUTTI. Well, there would be many things that would be necessary to be done simultaneously. But in case enzyme treatment should prove to be feasible, one of the earliest things that would be done would be to give the patient a sufficient amount of this substance to hopefully have some effect on the clot and to dissolve it.

Mr. FOGARTY. Well, the damage has already been done; has it not?

Dr. KNUTTI. The damage is done after the blood has been shut off from the heart muscle long enough to cause death of the tissue which the artery supplies. So in the very first stage of the thrombus formation and total occlusion, there may be time to prevent ultimate death of the tissue.

Mr. FOGARTY. Well, how long generally?

Dr. KNUTTI. Well, sir, I cannot answer that question directly. It depends on a number of factors. It depends on the collateral supply to the tissue, the other vessels that may supply the area.

Mr. FOGARTY. I would not expect you to have a precise time, but what is a good guess?

Dr. KNUTTI. Perhaps minutes—minutes to an hour or less. If there is no collateral circulation to this area, if the heart muscle itself is in not too good a condition to begin with, then it dies quicker than it would if there were collateral vessels and the myocardium and the patient as a whole are in good condition.

Mr. FOGARTY. I see. How do you know when you have had a coronary? Would you know if you had one?

Dr. KNUTTI. I do not know that I would. I think I would have to depend on the physician that came in to see me. They manifest themselves in many ways.

There is such a thing as a silent coronary in which a patient has an attack and shows ultimate signs of infarction without the pain that most frequently accompanies coronaries. And the pain itself is sometimes confused with pain in the epigastrium or in the stomach which is due to other causes; so in the past, many coronaries have been misdiagnosed because a physician thought that the patient had acute indigestion.

Mr. FOGARTY. I had one 11 years ago and I thought that is what I had, indigestion. I walked around with it for a week before I landed in the hospital, and I played golf a couple of times.

Dr. KNUTTI. Your myocardium was in good shape, sir.

Mr. FOGARTY. This new development is something real exciting, is it not?

Dr. KNUTTI. I think it is very important.

Mr. FOGARTY. That is how it hits me anyway. I am very much interested. Go right ahead.

Dr. KNUTTI. Among some of the other fields in which we have active or contemplated committees, are in the problems of hemophilia, cardiac catheterization, artificial organs—such as the mechanical heart to which I want to address myself a little later.

ADVANCES IN HEMOPHILIA

Mr. FOGARTY. You have made some advances in hemophilia during the last year or two, have you not?

This is just the opposite of what you are trying to do in connection with clot-dissolving agents, is it not?

Dr. KNUTTI. Yes. They both are a part of the total blood-clotting study, but in hemophilia we are interested in the isolation of a substance which will promote blood clotting. This is part of the general clotting-nonclotting-dissolving mechanism.

Mr. FOGARTY. There have been advances made in the last couple of years, have there not?

Dr. KNUTTI. A number of advances have been made.

Mr. FOGARTY. Do you want to tell us about them? There is more interest, I find, in the last 3 or 4 years in the problems of hemophilia than ever before.

Dr. KNUTTI. One of the factors which has been identified recently, among very many factors that have to do with blood clotting, which have numbers attached to them, is factor 8.

Mr. FOGARTY. Excuse me. On some of these examples that you give, you may be a little bit brief, but you may expand on them for the record.

Dr. KNUTTI. All right, sir.

Mr. FOGARTY. But you go ahead and tell us briefly.

Dr. KNUTTI. Factor 8 is what they call the antihemophiliac factor. Before this was discovered, if bleeding occurred in a hemophiliac, in order to attempt to stop it, they had to either give transfusions of whole blood or plasma, or certain plasma fractions. The rationale behind this was to give something that caused the hemophiliac blood to clot, and this was ultimately found to be factor 8, which was in these various substances that were used.

Since this has been isolated, it is hoped that enough of it can be produced not only to take care of patients, but to be used as a research tool in studying the mechanisms involved in hemophiliac and other blood-clotting mechanisms. In fact, this latter reason is why the Heart Institute is particularly interested in this particular field, since it has to do with the clotting mechanisms.

We are in the process of setting up a committee which is to advise us on the whole problem of hemophilia.

Then in the area of cardiac catheterization, this is being restudied to determine what its real value is, particularly focusing upon accidents that may occur during the catheterizing procedure. Apparently in this operation there are complications which do not get into the medical literature. So we are setting up a collaborative type of study by a number of centers to report the bad side effects of cardiac catheterizations.

Mr. FOGARTY. What are some of the bad side effects?

Dr. KNUTTI. Well, sometimes unqualified individuals or individuals who have not received sufficient training in putting a catheter up through a vein and into the heart itself may get into trouble for just mechanical reasons. Occasionally certain substances are used to inject into the bloodstream which may or may not have a bad effect on the patient. So the items being focused on are the mechanics of the procedure and the tolerance of the body for certain substances which may be used to visualize by X-ray or to estimate by means of counting devices, using radioactive isotopes. There has been a number of trials of various substances by various individuals in this country and we do not have all of the side effects documented, so that we can balance them against each other in order to find out what are really the most serious complications.

The smoking problem is just in the planning stage at this point, but we have called in an expert committee to discuss this problem and what the Heart Institute, in the general framework of possible Public Health Service activities, may do in furthering research in this field.

We believe that this activity of the Council and the Council's planning committee and these subcommittees composed of scientists is proving to be a very efficient and productive means for assessing areas in the cardiovascular field which show signs of promise and development, and we are indebted to a large number of individuals who have been helping us out in this respect.

(The additional information requested follows:)

HEMOPHILIA

The coagulation of blood is a complex process not yet completly understood. It entails a large number of steps and the participation of at least 11 clotting factors. The international system of nomenclature uses Roman numerals I–XII (with the exception of VI, for which no factor has yet been designated) to identify these clotting factors. An absence or deficiency of any of them can result in clotting abnormalities. It now appears that hereditary deficiencies exist for most of these clotting factors; and, with the exception of factors III, IV, and XII, such deficiencies result in hemorrhagic disease. The severity of the bleeding tendency usually depends upon the degree of the deficiency.

The blood clotting factors, the role they are thought to play in the coagulation process, and the abnormal bleeding states associated with clotting factor deficiencies are described in the appendix to this report.

Formerly, all of these bleeding tendencies were lumped under the general heading of hemophilia. However, today classical hemophilia (hemophilia A) denotes an absence or deficiency of factor VIII, whereas hemophilia B (also called Christmas disease) denotes an absence or deficiency of factor IX. These two diseases are the commonest of the 12 or so hereditary bleeding disorders discovered thus far, together accounting for about 90 percent of such cases.

HEMOPHILIA A

The commonest of the hereditary disorders of blood clotting, hemophilia A is inherited as a sex-linked recessive trait. Only males get the disease although females carry it. If a male hemophiliac begets children, his sons and daughters will be normal. However, the daughters will be carriers of the trait, and so their sons will have a 50–50 chance of being hemophiliacs like their grandfather.

The disease varies considerably in intensity, although, in general, the clinical severity of the disease and the plasma concentration of the deficient clotting factor are usually closely similar in affected individuals within any one family. In severe cases, factor VIII may be undetectable in the patient's plasma, and massive hemorrhage may result from the slightest trauma, frequently causing permanent and incapacitating tissue damage or even death. In mild cases, factor VIII activity may be as high as 15 to 25 percent of normal, and the patient may experience massive bleeding episodes only after relatively severe injury or surgery.

Mild hemophilia appears to be far more prevalent than severe hemophilia. Many cases may go undetected until the victim undergoes surgery for some unrelated disorder. Until recently, although the surgeon might rue the fact that routine tests of bleeding and coagulation time were inadequate to screen out such potential bleeders, he also had to face up to the fact that a complete hemostatic study required many time-consuming and costly tests that were not practical for routine screening.

A relatively simple procedure that appears to have overcome this problem is the partial thromboplastin time test, developed by NHI grantees at the University of North Carolina.

Blood is drawn into a syringe containing sodium citrate (an anticoagulant), then centrifuged to separate the plasma. To a small sample of this plasma is added calcium chloride and a phospholipid extract. The time required for the first appearance of fibrin threads (indicative of clotting) in the test tube is recorded with a stopwatch. This simple test will detect all clinically important clotting factor deficiencies except factor VII.

A factor VII deficiency is readily detected by a test of prothrombin time, which is run in the same way as the partial thromboplastin time except that a tissue extract is substituted for the phospholipid extract.

The two tests cover the possible gamut of clotting factor deficiencies. If either test is abnormal, then a clinically significant hemorrhagic state exists and it becomes necessary to identify the missing or deficient factor. This is done by matching experiments in which plasmas or plasma fractions known to be deficient in specific clotting factors are added to the abnormal plasma and the tests repeated. If the known plasma sample fails to correct the abnormal test, then it can be assumed that both are deficient in the same clotting factor.

When severe blood loss has occurred or is anticipated because a surgical procedure is to be performed, the hemostatic defect of hemophilia A can be temporarily corrected by transfusions of blood, plasma, or a suitable fraction of plasma. Whole blood is preferably not used except to replace shed blood. The use of whole blood merely to raise plasma levels of factor VIII might also dangerously increase the patient's blood volume, greatly increase the risk of transfusion reactions, and raise the body's iron stores to excessive levels. When whole blood transfusions are required, only the freshest blood can be relied upon as a source of factor VIII because this factor deteriorates rapidly during storage.

Plasma does not provide nearly so many problems as does whole blood. When collected with care, immediately centrifuged and frozen, and stored at —30° C., plasma will retain over 80 percent of its original factor VIII activity for as long as 4 months. However, once thawed, plasma must be used immediately because its factor VIII activity declines very rapidly thereafter.

To "prime" a patient with hemophilia A for surgery or to control bleeding from accidental wounds and surgical incisions, his plasma factor VIII concentration must be brought up to 30 percent or more of normal and sustained at this level for many hours and even days. This takes a lot of plasma. Even when the patient is not bleeding, about half of the transfused factor VIII disappears within 10 hours; in bleeding patients the rate of disappearance is much faster.

The large quantities of plasma that may be required to maintain factor VIII concentrations at therapeutic levels can raise circulating plasma volume to excessive levels and produce cerebral edema or cardiac embarrassment. This problem has led to a great deal of effort to prepare concentrates of factor VIII suitable for therapeutic use.

Recently a concentrate has been produced which contains about 7 times as much factor VIII as an equal volume of plasma. In extensive clinical trials the concentrate has usually proved to be effective in controlling bleeding after surgery or severe injury. Although a significant advance in the therapy of hemophilia, the concentrate nevertheless has its drawbacks. For one thing, its potency fluctuates widely from batch to batch so that dosage schedules must be adjusted to the particular lot being used or else administered on a hit or miss basis. Also, potentially serious complications have occasionally attended its use. Some of these difficulties appear to stem from the large quantities of fibrinogen also present in the concentrate. Elevated blood fibrinogen levels can cause sludging and breakdown of blood cells.

Current studies indicate that chromatography of the plasma concentrate on cellulose columns yields a highly purified fraction containing very little fibrinogen. Animal studies have shown that the fraction is potent and nontoxic, and it has been used successfully in a number of hemophiliacs in conjunction with tooth extractions.

Sterilization problems have hindered the large-scale production of factor VIII concentrates. At present, the material must be prepared aseptically or else the final product must be passed through a sterilizing filter just before being sealed in ampoules. Aseptic preparation is time consuming and costly, whereas filtration results in significant losses of factor VIII activity.

NHI grantees report that the plasma fraction can be rendered bacteriologically sterile without any significant loss of factor VIII activity by treatment with a compound called beta-propiolactone. The beta-propriolactone treated fraction still retains its stability when irradiated with ultraviolet light. The combined treatment is also thought to destroy any contaminating viruses, although this has not yet been demonstrated conclusively. If so, this could be an important advance against a very worrisome problem of blood-replacement therapy: the threat of hepatitis due to infected blood or blood products.

The factor VIII concentrate has another important drawback: it is very, very expensive. Enough concentrate for a single operation usually costs $2,500 and up. However, improved production methods may bring the price down.

Factor VIII preparations can be obtained from animal blood, and these have been used successfully in preparing hemophilic patients for surgery. Unfortunately, these preparations are antigenic and anaphylactic; thus they are strictly one-shot measures, and even so may cause severe reactions.

NHI grantees have reported that a procoagulant called fraction P, obtained from human urine, normalizes in vitro coagulation of blood from hemophiliacs. When applied topically, the fraction effectively stanched bleeding from wounds resulting from accidents, tooth extractions, or surgery, reducing the number of transfusions required or making them unnecessary. In several patients the substance was administered orally in an attempt to control intestinal hemorrhage, but the results were inconclusive.

The ability of urine to normalize clotting of hemophilic blood has been known for many years, but only recently has the active principle been isolated and some of its properties determined. In its action and in its requirements for cofactors, fraction P somewhat resembles factor VIII. This suggests that it might be useful against massive bleeding episodes or during surgery in hemophilia. The fraction is readily extracted from urine, is stable enough to withstand sterilization by heat immediately before use, and has demonstrated a low level of toxicity in animal studies. The grantees feel that the therapeutic potential of fraction P deserves further consideration.

HEMOPHILIA B

Hemophilia B, or Christmas disease, is one-fifth to one-tenth as common as hemophilia A. It closely resembles hemophilia A in its clinical manifestations and its inheritance. It too is a sex-linked recessive trait passed on by heterozygous mothers to their affected sons. Usually the clinical severity of the disease correlates well the degree of the factor IX deficiency. However, female carriers may show a marked reduction in factor IX, yet withstand considerable trauma without serious bleeding; whereas their sons, who may have a less marked deficiency, often bleed more easily and seriously.

Factor IX appears to be synthesized in the liver. In addition to the hereditary disease, factor IX deficiency can result from a deficiency of vitamin K, from certain liver diseases, and from the use of coumarin-type anticoagulants.

Treatment of hemophilia B consists of replacing the missing factor IX. This may be done with transfusions of whole blood, plasma, or factor IX concentrate. Concentrates with 5 to 20 times the factor IX activity of normal serum have been prepared by several groups and have proved to be effective; but these concentrates are not generally available and so plasma transfusions remain the treatment of choice.

Fortunately, factor IX is relatively stable. Ordinary banked blood is a suitable source, and plasma prepared from banked blood retains all of its factor IX activity for several months when stored at —20°C.

When factor IX is transfused, 20–40 hours elapse before half of it has disappeared, versus 10 hours or less for factor VIII. Surprisingly, however, as much plasma and sometimes more is needed to promote hemostasis in hemophilia B as in hemophilia A. It appears that part of the transfused factor IX does not remain within the circulatory system, but becomes distributed within a relatively large extra-vascular pool. Thus, as in the case of transfusion therapy for hemophilia A, hypervolemia with cerebral edema and cardiac embarrassment may complicate the treatment of hemophilia B.

CONCLUSION

The management of hereditary disorders of blood coagulation has improved considerably during recent years as a result of better diagnostic techniques, the delineation of a number of different hemorrhagic states formerly thought to be hemophilia, and the availability for therapy of blood and blood products. Still, much remains to be done. Thus far, no therapy other than replacing the missing or deficient clotting factor has proved effective against these disorders; and since factor VIII and factor IX cannot yet be obtained in pure form, the therapy of hemophilia has relied on whole blood, plasma, or plasma fractions. This has meant transfusing a lot of other unwanted substances along with the missing factor and so increasing the likelihood of transfusion complications.

To make matters still more complicated, some hemophiliacs develop circulating anticoagulants, possibly as a result of repeated transfusions. These anticoagulants appear to be enzymes directed specifically against factor VIII or IX. Such patients thus become unresponsive to further transfusion therapy.

Research directed toward the solution of these and other problems posed by these diseases should be greatly facilitated as a result of the establishment at several research institutions of colonies of dogs with hemophilia and other inherited bleeding disorders closely resembling those of humans. These colonies should be of incalculable value to research on genetic, physiological, and biochemical aspects of hemophilia as well as the development and evaluation of new or improved therapeutic techniques.

Appendix

COAGULATION

For convenience, the coagulation of blood may be considered to occur in three stages:

(1) *Two types of thromboplastin are generated.*—Intrinsic thromboplastin arises from the interaction of a number of plasma constituents: the process requires factors IV, V, VIII, IX, X, XI, and XII. Blood platelets and contact with a foreign surface are also necessary for this interaction to occur. Extrinsic thromboplastin arises from the reaction of some plasma factors with tissue juices present at injury sites. The process requires the tissue juice and factors IV, V, VII, and X.

(2) *Thromboplastin catalyzes the conversion of prothrombin to thrombin.*—Free thrombin is never present in the blood, since its presence is incompatible with life. Instead the blood contains considerable quantities of an inactive precursor, prothrombin, from which thrombin is generated as needed to initiate clotting. Excess thrombin is quickly neutralized by inhibitors in plasma or by adsorption onto the fibrin of blood clots.

(3) *Thrombin converts fibrinogen to fibrin.*—Fibrinogen consists of three globular parts connected by peptide chains like beads on a thread. Thrombin breaks off one of these beads. The two-bead units then link together in chains (polymerize) to form fibrin, the structural substance of blood clots.

BLOOD CLOTTING FACTORS

Factor I (fibrinogen) is an unstable, soluble protein formed in the liver. It is the precursor of fibrin, the structural substance of blood clots. Congenital afibrinogenemia is a rate disorder in which the plasma lacks detectable quantities of fibrinogen. It affects both sexes. Bleeding episodes are seldom spontaneous, but are usually the result of injury. Surprisingly. excessive menstrual bleeding (menorrhagia) is uncommon among females with the disorder. Treatment consists of transfusing fibrinogen, preferably by means of plasma concentrate.

Factor II (prothromin) is also made by the liver. Vitamin K is required for its synthesis. Prothrombin is the precursor of thrombin, the protein-digesting enzyme acting in the formation of fibrin. A hereditary deficiency of prothrombin causes a bleeding tendency resembling hemophilia. The deficiency can occur in women, in whom menorrhagia may be a frequent and often disabling complication. Hormones may be used to suppress menstruation in affected women. No specific therapy is available, and so blood or plasma transfusions are the treatment of choice. The administration of vitamin K is not effective as a therapeutic measure.

Factor III (extrinsic thromboplastin) is a phospholipid complex found in tissue juices and extracts. It aids in the conversion of prothrombin to thrombin.

Factor IV (calcium) acts as a bonding agent in the formation of thromboplastin and is also essential to the conversion of prothrombin to thrombin. There is no hemorrhagic disorder associated with calcium deficiency, since such a severe calcium deficit would be incompatible with life.

Factor V (proaccelerin), a protein synthesized by the liver, aids in the formation of intrinsic thromboplastin and in the conversion of prothrombin to thrombin. A factor V deficiency causes a disease known as "parahemophilia," with clinical manifestations similar to those of classical hemophilia. Both sexes are affected. In women, menorrhagia and severe hemorrhage after childbirth are serious complications. Treatment entails transfusion of fresh or freshly frozen plasma. In females the use of hormones to suppress menstruation has not been reported, but may be of value.

Factor VII (proconvertin) is a stable plasma and serum protein synthesized by the liver. Vitamin K is needed for its synthesis. It is not consumed during clotting, but is essential for the generation of extrinsic thromboplastin. Factor VII deficiency can cause a moderately severe hemorrhagic disease resembling hemophilia; however, some individuals with severe deficiencies may have no trouble with bleeding episodes. Plasma transfusions are the treatment of choice. The administration of vitamin K is generally useless as a therapeutic measure.

Factor VIII (antihemophilic factor) is a relatively unstable plasma protein essential to the formation of intrinsic thromboplastin. Deficiency causes hemophilia A (classical hemophilia).

Factor IX (plasma thromboplastin component, Christmas factor) is a relatively stable plasma and serum protein essential for intrinsic thromboplastin generation. It is not consumed during clotting. Deficiency causes hemophilia B (Christmas disease).

Factor X (Stuart-Prower factor) is a stable plasma and serum protein that participates in the generation of intrinsic and extrinsic thromboplastin and also in the conversion of prothrombin to thrombin. Deficiency produces a hemophilia-like bleeding tendency that affects both sexes. Menorrhagia is often severe in affected women; but, in one reported case, remission occurred during pregnancy. There is no specific therapy, and so blood or plasma transfusions are the treatment of choice.

Factor XI (plasma thromboplastin antecedent) is a stable plasma and serum protein essential for generation of intrinsic thromboplastin. It is not consumed during coagulation. Deficiency is rare, but affects both sexes with equal frequency. Spontaneous bleeding is uncommon, but serious bleeding may occur after surgery, injury, or tooth extractions in individuals with severe deficiency. Individuals with minor deficiency have only minor symptoms or none at all. The value of blood or plasma transfusions in correcting the deficiency is not clear, but these measures are used during bleeding episodes and also to "prime" affected individuals for surgery.

Factor XII (Hageman factor) is a surface activator. A deficiency may cause gross abnormalities in blood tests because it is necessary for the clotting of blood in glass test tubes. However, the deficiency seldom causes any bleeding problems in affected individuals.

CONFERENCE ON CARDIOVASCULAR DISEASE

Now, sir, if I may say a word about other plans that are being made, the next one I mention is the conference, which is to be held in 1965. The First National Conference on Cardiovascular Disease was held in 1950, in January. The Heart Institute had not been established very long at that point. In the years since, and it will be 15 years by the time the second one is held, the Heart Institute Directors have brought to this committee brief accounts year by year of our activities and some indications of research progress, opportunities, and benefits.

That conference in 1950 summarized the status of our knowledge at that time. But in 15 years we have come a long way. We felt 2 years ago that the time had come to start planning for a second such conference to bring us up to date.

Now, as you mentioned, sir, the detailed planning for the conference is under the direction of Dr. E. Cowles Andrus, who is professor emeritus of medicine at Johns Hopkins and a very distinguished cardiologist. He is also past president of the American Heart Association and was on the National Advisory Heart Council for at least two terms. Dr. Andrus is the conference director.

The direct planning for this has now been going on for over a year. The conference director has invited approximately 40 scientists, teachers, and other knowledgeable individuals to help design and prepare, with the assistance of other collaborators, a comprehensive report on the subject of the conference; namely, cardiovascular disease—and to project special opportunities and urgent needs for the future in research and training, and application of new knowledge.

At the present time, in addition to the 40 scientists who are heading up sections, there are 375 leaders in their specialties who are participating in the preparations for this conference. There is a list of many disciplines represented in this, I should say maybe 20 or 25. I will tell you but a few of them for the sake of time: Internists, radiologists, surgeons, pathologists, pharmacologists, pediatricians, hemotologists, anatomists, geneticists, biochemists, and so forth. There are going to be panels discussing all of these basic and clinical disciplinary areas.

Also there will be heart disease control specialists and rehabilitation experts, medical and nursing educators, because this conference is being sponsored not only by the Heart Institute, but by the American Heart Association and by the heart disease control program of the Public Health Service Bureau of State Services.

In very broad terms, among the purposes of the conference are: to provide an impetus to and strengthen the resources of the nationwide attack on heart disease in toto; to reduce more greatly the Nation's burden of death and disability from cardiovascular disease than is now possible by means of mechanisms that will be developed from the conference; to summarize and assess cardiovascular progress as it may stand in the year 1965 in comparison with the year 1950; to define and recommend areas and directions for research which are likely to produce new fundamental and basic and clinical knowledge for greater progress; and to determine and recommend how to increase and improve the application of knowledge and to develop and to widely publish and to disseminate for the professions, the interested agencies, and the public, the proceedings and recommendations of the conference.

The conference plans are being designed to provide a continuum of followup to consider, modify, or to suit varying local needs and resources, and to adopt and implement the information and results and recommendations of the conference, especially in the field of community services, but the followup also would have to do with recommendations to research-supporting agencies as to the needs and the directions in the field.

Out of the conference we expect to see an assessment of where we stood 15 years ago, where we stand today, and some intelligent projections as to where we might stand in the next 10 or 15 years along with specific recommendations for implementation of programs.

It should also document, I think, in striking terms, results of the stimulus afforded the cardiovascular programs by the actions in the past and present of this committee. I am sure that it will be a meeting that this committee will find of great interest.

SUMMARY OF STATEMENT

Mr. Chairman, this concludes my opening comments, but, in summarizing my statement, I would like to add that during 1963 diseases of the cardiovascular system killed an estimated 990,000 Americans. Over half of these lives were claimed by coronary heart disease, which continues its undisputed reign as our Nation's leading killer. These mortality figures are appalling; still, providing some relief to this dark picture are statistics indicating that among women under 55 the death rate from coronary heart disease has dropped substantially, while among white males it appears to be leveling off and is actually on the wane in some age groups. Meanwhile, death rates from hypertension, strokes, and rheumatic heart diseases have continued to decline.

Our main hope for reducing the heavy toll levied upon our population and economy by these diseases lies in continuing our vigorous research assault upon them. The buildup of scientific knowledge is continuing in all quarters. In some areas, spectacular gains have been made; in others, the going has been heavy and progress slower.

For example: The use of compression chambers containing oxygen under pressure and the widespread application of improved life-support techniques are making possible ambitious surgical procedures, such as multiple valve replacement, that could not have been attempted only a few years ago. Better techniques for pinpointing coronary-artery obstructions and improved methods of small-vessel surgery show promise of increasing the benefits and reducing the formerly prohibitive risk of surgery to improve severe coronary heart disease. Epidemiological and laboratory studies continue to amass information that may help to solve the riddles posed by atherosclerosis and perhaps lead to effective means of prevention or cure. And though the causes of essential hypertension have continued to elude us, this has not prevented the development of improved means of controlling the disease. Meanwhile, through our training grants and fellowship programs, additional scientific manpower continues to be mobilized against the cardiovascular diseases.

Mr. Chairman, the request for the National Heart Institute is $125,398,000 as compared with the $116,047,000 available in 1964. The increase of $9,351,000 will provide an additional $8,791,000 for research grants and $198,000 for training grants. The balance of the increase will provide for strengthening review and approval activities, for built-in costs of the pay increase, and for support of central services.

Mr. Fogarty. Thank you, Doctor.

1965 BUDGET

Taking all the adjustments into consideration, you have $116,231,000 available for 1964 and the request for 1965 is $125,398,000, plus an unobligated balance carried forward of $559,000. This would make an increase of $9,726,000.

PLANNING GERONTOLOGICAL RESEARCH FACILITIES

The unobligated balance of $559,000 is the unobligated balance of funds appropriated for fiscal year 1962 to plan your gerontological research facilities. So you still are not going to have this planning done by the end of 1964, is that right?

Dr. KNUTTI. No, sir. Although the planning at the present time is progressing at what we believe is an extremely reasonable rate.

We had, as I testified before this committee last year, some impediments in getting this program started. But at the present time the architects and engineers have been selected and everything is moving in accordance with the GSA schedule that has been set up for it.

Mr. FOGARTY. How much of the $1 million appropriated in calendar year 1961 have you obligated as of now?

Mr. HENSCHEL. $256,532.

UNOBLIGATED BALANCE

Mr. FOGARTY. You propose to transfer $3,457,000 to other parts of the Public Health Service for pay costs and still have an estimated unobligated balance of $7,845,000. This is a total of $11,302,000 that you told us last year you needed and now you tell us you do not. What is your explanation for this?

Dr. KNUTTI. Well, sir, this represents an unprogramed reserve at the time it was decided upon, which was early in the fiscal year. In other words, at that point, we were looking forward to some programs which had not yet been implemented.

Mr. FOGARTY. Could they be implemented now?

Dr. KNUTTI. I think it will be possible to implement some programs; yes, sir.

ADDITIONAL PROGRAMS FOR IMPLEMENTATION IN 1964

Mr. FOGARTY. Well, will you supply for the record all the programs you think could be implemented in this fiscal year?

Dr. KNUTTI. Yes, sir.

(The information requested follows:)

Additional programs for implementation in 1964

A. PROGRAMS READY FOR IMMEDIATE IMPLEMENTATION

Purpose	Amount	Method of funding	Remarks
Deficit for financing competing continuations for balance of 1964.	$2,000,000	Regular research grant projects.	Pending release of unprogramed funds; anticipated approval by National Advisory Heart Council, March 1964.

B. PROGRAMS TO BE READY FOR IMPLEMENTATION DURING THE REMAINDER OF 1964

Cooperative study of drugs and coronary heart disease.	$800,000	Research grants and related contracts.	Pending release of unprogramed funds and other clearances.
Development of artificial hearts	420,000	Research grants	Pending release of unprogramed funds and special council approval.

C. SUMMARY

Presently unprogramed funds (reserve)	$7,845,000
Programs ready for immediate implementation	−2,000,000
Programs to be ready for implementation during the remainder of 1964	−1,220,000
Estimated unexpended balance, 1964	4,625,000

RESEARCH GRANTS FOR 1965

Mr. FOGARTY. Now, the only significant increase you are budgeting for 1965 is $8,791,000 for research grants, but most of that is for increased overhead allowance and to continue projects already started. I notice, on page 211, you show that you actually will not be able to support as many new projects in 1965 as in 1964.

Dr. KNUTTI. That is correct, sir.

Mr. FOGARTY. So even though heart disease kills more people than all other diseases put together, we are not going to be able to keep up the momentum in research grants in 1965. We are leveling off—in fact we are going backward if we are not going to fund as many new projects in 1965 as we did in 1964.

Dr. KNUTTI. Well, we feel that this budget will give us the opportunity to carry on the programs that have been developed to date.

Mr. FOGARTY. It is a leveling off as I look at it.

I am not blaming you, but I think this is one of the worst budgets that I have seen in the whole Public Health Service. It is one of the most backward-looking budgets and one of the most conservative that has ever been sent to this committee.

ADVANCES IN HEART RESEARCH

Now, would you supply for the record a statement on research advances in:

1. Hypertension.
2. Atherosclerosis, including research regarding hormonal effects.
3. Effect of diet on heart disease.
4. Development of prosthetic hearts.
5. Correction of congenital defects.
6. Blood coagulation defects.

Dr. KNUTTI. Yes, sir.

(The information requested follows:)

HYPERTENSION

Although the death rate from hypertension has dropped appreciably during the past 10 years, health statistics indicate that hypertension, with or without heart involvement, killed some 75,000 Americans during 1962. Not expressed in this figure is the probably substantial contribution made by hypertension to the 527,561 deaths due to heart disease and to the nearly 200,000 deaths due to strokes.

The economic toll exacted annually by hypertension has not been worked out in dollars and cents, but it is heavy indeed. For example, data from the 1957–58 health survey indicate that hypertension caused the loss of 9.5 million working days among the usaual working population and resulted in an additional 99 million days of restricted activity. Again not expressed in these figures is the role played by hypertension in the 16.5 million lost working days and the 238 million restricted activity days resulting from heart disease and other cardiovascular conditions often closely associated with high blood pressure.

WHAT IS HYPERTENSION?

Most cases of high blood pressure fall under the classification of "essential hypertension," which is defined as a chronically elevated diastolic blood pressure (exceeding 95 millimeters of mercury) that cannot be blamed on anything specific. This distinguishes "essential hypertension" from "secondary hypertension," which might result from such factors as (1) pheochromocytoma, a secreting tumor that frequently raises blood pressure by releasing large quantities of norepinephrine, a powerful blood vessel constrictor and metabolic stimulant; (2) such kidney disorders as nephritis and nephrosis, dropped kidneys, and congenital or acquired obstructions to renal blood flow—all of which may cause the kidney to release renin, which, in the blood, catalyzes the formation of angiotensin, another powerful blood vessel constrictor; (3) primary or secondary aldosteronism, in which the excessive secretion by the adrenal cortex of aldosterone, a hormone that promotes salt and water retention, frequently raises blood pressure by expanding blood and plasma volume; (4) atherosclerosis, which frequently causes increased systolic blood pressure because of disease-induced losses in blood vessel elasticity; and other rarer causes.

WHAT CAUSES ESSENTIAL HYPERTENSION?

The cause or causes of essential hypertension remain an enigma. For a time, hypertension was thought to be a compensatory mechanism to insure that the tissues received adequate amounts of blood as the person grew older and the normal blood-carrying capacity of his blood vessels diminished. This hypothesis has been adbandoned, and it is now generally accepted that hypertension is a disease entity. However, though many theories have been advanced to explain how it arises, none has yet accumulated enough supporting evidence to become generally accepted.

Some scientists blame an upward reset of the carotid sinus and other baroreceptors, which ordinarily act to stablize blood pressure at normal levels through their effects on heart rate, heart output, and blood vessel caliber. Others blame the kidney—not the reninangiotensin response triggered by renal blood deprivation, but the failure of the kidney to secrete sufficient quantities of some still-mysterious hormone that ordinarily acts to maintain normal blood pressure. Still others blame derangements in the metabolism of certain amines, such as norepinephrine, epinephrine, tyramine, and others, which are postulated to play some essential role in blood pressure regulation. Currently, most scientists probably subscribe to the "mosaic concept," which assigns no specific cause to hypertension, but maintains that all of the aforementioned factors, and possibly others, may operate in the development of hypertension and in the various phases of the disease.

THE PREVALENCE OF HYPERTENSION

An extensive study conducted by 26 life insurance companies among some 4 million policyholders over a 20-year period indicated that about 1 percent of teenagers, 10 percent of men in their forties, and 25 percent of men in their sixties suffer from hypertension. Although it has not been demonstrated conclusively, the clinical impression of many scientists is that women are more often afflicted than men; and, in many series, the number of female subjects is usually about twice the number of men. However, though women appear to be more often affected, men appear to be subject to severer forms of hypertension and to suffer a higher proportion of its murderous consequences: strokes, heart attacks, and congestive heart failure, and renal complications.

RISK FACTORS IN HYPERTENSION

In a study conducted by the Metropolitan Insurance Co., 3,343 office ememployees over 40 were divided into three groups: those with persistently normal blood pressure (diastolic pressures below 90), those with frequent elevations in diastolic pressure, and those with consistently elevated diastolic pressure. These subjects were followed for an average of 15½ years. The study showed that, as the frequency of elevations of diastolic pressure increased, so did the number of cardiovascular-renal complications, the rate being three to five times as high in those with persistently elevated diastolic pressures as in the normotensives.

The Framingham study indicates that hypertension is certainly a major factor in the development of coronary heart disease, and that heart disease risk increases progressively with increases in blood pressure. This gradient of risk appears to apply even in the so-called normal range of blood pressure: for example, in going from systolic pressures of less than 120 to pressures exceeding 180, there is a sevenfold increase in heart disease risk. Hypertension is an especially serious factor when compounded by excessive serum cholesterol levels, since there is abundant evidence that hypertension hastens the deposition of cholesterol and other serum lipids in the blood vessel wall.

There is also a strong association between obesity and hypertension. A Chicago study showed that, in men 50 to 59, weight 15 percent or more over desirable weight is associated with a twofold to threefold increase in hypertension. Data from the Framingham study indicate that the twofold increase in heart disease risk associated with weights 30 percent or more over desirable weight is primarily the result of the increased blood pressure associated with obesity.

THE NATURAL HISTORY OF HYPERTENSION

Most victims of hypertension develop the disease during their thirties. Nearly all victims pass through a transitional phase, usually lasting several years, during which their blood pressure rises above normal only occasionally, then more and more frequently, finally remaining at hypertensive levels. The earlier medical histories of hyptertensive patients are usually marked by variability of blood pressure and occasional high readings. Even a single high reading during youth is cause for some concern, since such elevations appear to be associated with a threefold to fivefold risk of developing hypertension during middle age.

If untreated, hypertension usually runs a 20-year course, most often terminating fatally during the victim's fifties. During msot of its course, hypertension produces few symptoms, but during the last third there is usually progressive failure of such organs as the heart, brain, or kidney—alone or in combination and at variable rates. Hypertension produces its adverse effects by increasing the workload of the heart, producing widespread blood vessel damage, and by accelerating the development of atherosclerosis. Thus the effects of hypertension are often manifested in heart attacks and strokes as well as in heart of kidney failure.

In some cases, hypertension progresses into a malignant phase in which diastolic pressure rises to very high levels, eventually producing severe renal damage and progressive renal failure. If untreated, malignant hypertension is usually fatal within a year.

THE EFFECTS OF TREATMENT

Today the armamentarium of the practicing physician is well stocked with drugs found to be effective for reducing blood pressure in hypertensive patients. What sort of results have been achieved with these drugs? Long-term, carefully controlled studies indicate that drug therapy is of great value in the treatment of severe hypertension, especially the malignant phase of the disease, and is of definite value in those cases of hypertension with evidence of cardiac, renal, cerebral, or vascular involvement.

For example: In one study, mortality from malignant hypertension was reduced by drug therapy from 100 to 17 percent. In cases of severe and moderately severe hypertension, 5-year mortality was 61 percent in untreated patients, but only 18 percent in the drug-treated group. Further, the reduction in diastolic pressure produced by the drugs also effectively arrested renal vascular deterioration in these patients. In another study among patients aged 50 to 54 suffering from moderate hypertension, mortality was 49 percent in untreated patients versus 25 percent in the treated group. The reduced mortality resulted primarily from a reduction in such complications of hypertension as strokes and congestive heart failure.

Not yet available are results of long-term studies evaluating the effectiveness of drug therapy in milder cases of hypertension treated over longer periods of time, but there would appear to be ample grounds for optimism.

SOME DRUGS AND THEIR MECHANISMS OF ACTION

A substance that appears to be the key to the blood pressure effects of many drugs currently used against hypertension is norepinephrine. In the sympathetic nervous system, norepinephrine is the chemical transmitter (neurohormone) liberated by sympathetic nerve impulses to convey their messages between nerve terminals and their target organs. Sympathetic discharges can liberate norepinephrine to interact with receptors in the blood vessel wall and cause constriction of that vessel; or it can be liberated in the heart to speed up heart rate and output. All of these actions tend to raise blood pressure.

NHI studies have shown that a number of hypotensive agents currently in clinical use act to reduce the flow of nerve traffic in the sympathetic nervous system by interfering with the storage, release, or metabolism of norepinephrine.

Reserpine and its analogs.—Reserpine and analogs such as syrosingopine lower blood pressure by striking at the mechanisms which maintain norepinephrine stores at sympathetic terminals. Here, high concentrations of norepinephrine are maintained by an active transport mechanism that prevents the amine from diffusing passively out of the storage site. Reserpine and its analog knock out this mechanism, allowing large quantities of norepinephrine to escape from the relative safety of the storage site. Most of it is promptly set upon and destroyed by the enzymes monoamine oxidase and catechol-O-methyl transferase. The heavy drain on its norepinephrine stores eventually depletes the nerve terminal of so much of its norepinephrine that too little remains to handle sympathetic nerve traffic.

The blood pressure effects of reserpine and its analogs stem from their ability to deplete norepinephrine stores at peripheral nerve endings. However, in only slightly larger doses, these drugs also deplete norepinephrine and serotonin stores in the brain, producing unwanted sedation and parasympathetic effects, and also release serotonin in the gut, frequently causing gastrointestinal disturbances and diarrhea. A problem in treating hypertensives with resperpine is the maintenance of dosage schedules that hold blood pressure down without eliciting these side effects. Certain of the reserpine analogs exert a somewhat more specific peripheral action than does reserpine, but these compounds share with reserpine a common feature that makes all these drugs relatively difficult to handle clinically.

Reserpine and its analogs are hit-and-run drugs; that is, they exert an effect that may persist long after the drug itself has vanished from the body. Thus, though all measurable amounts of reserpine may vanish from the brains of rabbits within 2 to 4 hours after a sedative dose, sedative effects may persist for more than 48 hours. For this reason, reserpine and its analogs must be administered clinically in small daily doses to allow its blood pressure effects to build up very gradually. Even so, there is some risk that desired levels may be exceeded and excessive sedation produced—an effect that cannot be immediately corrected by simply discontinuing the drug.

Guanethidine (CIBA), like reserpine and its analogs, affects blood pressure by acting on peripheral sympathetic terminals, but this action is much more specific. The drug does not affect brain amines (because it cannot readily get through the blood brain barrier), thus it does not cause sedation. It does not release serotonin in the intestines, and thus produces few gastro intestinal disturbances. It is stable in the gut and is relatively well absorbed, so it is suitable for oral administration.

Like reserpine, guanethidine releases norepinephrine from storage sites at sympathetic nerve terminals; but it differs in its mechanism of doing so, and norepinephrine depletion may not be the key to its hypotensive action. NHI studies indicate that guanethidine may release norepinephrine by persistent activation of the same mechanism through which the nerve impulse liberates the amine. However, unlike nerve traffic, which allows the nerve terminal and receptor to recuperate somewhat between pulses, guanethidine never lets up. While guanethidine can eventually deplete sympathetic terminals of norepinephrine, NHI studies indicate that the drug produces effective sympathetic blockade long before this occurs. This blockade may be due to a persistent depolarization resulting from the drug's unrestrained release of norepinephrine.

Alpha-methyl DOPA (Aldomet, Merck) first attracted research attention because of its ability to inhibit an enzyme, DOPA decarboxylase, whose action is essential to the synthesis of norepinephrine, epinephrine, and other vasoactive amines. Since certain of these amines are thought to play some nefarious role in hypertension, it was hoped that the use of decarboxylase inhibitors to block catechol amine synthesis might prove a promising new therapeutic approach. However, for several years after its synthesis in 1953, alpha-methyl DOPA was of interest only as a research tool for studies on amine metabolism, since neither it nor any of its chemical relatives demonstrated any effect whatsoever on blood pressure in animal studies.

Despite the absence of any demonstrable blood pressure effects in animals. NHI scientists became interested in alpha-methyl DOPA in 1958. They felt that it might possibly be useful for the treatment of pheochromocytoma or malignant carcinoid. These tumors are characterized by the production and secretion of very large amounts of norepinephrine and serotonin, respectively. The enzyme inhibited by alpha-methyl DOPA is essential to the production of both amines.

The drug was generously supplied to NHI by Merck Sharp & Dohme, whose scientists also collaborated with the NHI investigators in a series of careful toxicity studies in animals. The results indicated that alpha-methyl DOPA was nontoxic; so the NHI scientists cautiously tested the drug in some patients with pheochromocytoma or malignant carcinoid. Parallel biochemical studies were also undertaken in several patients with hypertension.

An thus it was, in 1959, that NHI scientists more or less "accidentally" discovered that alpha-methyl DOPA lowered blood pressure in hypertensive patients. All animal studies had indicated that the drug was useless as a hypotensive agent; the patient studies proved otherwise. Had this drug not been tested in humans, it might even today be considered simply another research tool for studies in amine metabolism. Instead, under the trade name Aldomet, the drug has proved to be a valuable new addition to the physician's arsenal of drugs against hypertension.

Concurrent with further clinical evaluation of alpha-methyl DOPA, the NHI scientists undertook biochemical studies aimed at clarifying the drug's mechanism of action. The findings indicated that alpha-methyl DOPA was actually ineffective at performing the task for which it was originally designed: blocking catechol-amine synthesis in the body. It appears that the tissues are far too well equipped with decarboxylase enzymes for even a very potent inhibitor to make any appreciable dent in their catechol amine production.

Instead, the studies have shown, the hypotensive effects of the drug probably stem from its ability to deplete norepinephrine stores in the sympathetic nervous system. This norepinephrine-depleting action apparently results, not from a direct action of the drug, but from metabolites arising from the action of decarboxylase on alpha-methyl DOPA. Two metabolites—alpha-methyl-dopamine and alpha-methyl-norepinephrine—have been identified; and either or both may mediate the blood-pressure effects of the drug.

The NHI clinical studies with alpha-methyl DOPA indicate that the drug effectively controls blood presure in hypertension of all degrees of severity in about two-third of the cases. (For unknown reasons, about one-third show only a slight response to the drug, or no response whatever.) Its performance has been particularly effective in patients with severe hypertension, including the malignant phase of the disease. Its high potency, smoothness of action, and relative freedom from toxic side effects make alpha-methyl DOPA the drug of choice in many hypertensive patients.

The drug frequently lowers blood pressure in both the supine and standing positions (although the latter effect predominates) and often reduces heart rate. It also produces mild sedative and tranquilizing effects, especially in very early phases of treatment. These effects usually subside with further treatment, and seldom impair proficiency in ambulatory patients.

Alpha-methyl DOPA does not cause the bowel disturbances that frequently attend the use of other hypotensive agents, nor does it cause sexual impotence in the male, except infrequently in patients receiving very high doses of the drug. The drug also does not produce the sudden, unexpected falls in blood pressure sometimes observed with other hypotensive agents, especially when the patient arises in the morning.

Monoamine oxidase (MAO) inhibitors block the action of an enzyme largely responsible for inactiviating norepinephrine, epinephrine, and a number of other biologically active amines. Although nobody could explain why slowing the destruction of such powerful stimulants as norepinephrine should somehow lower pressure, there did appear to be a direct relationship between the potency of these drugs as MAO inhibitors and their potency as hypotensive agents.

However, recent studies by NHI scientists disclosed a previously unsuspected action of MAO inhibitors that provides a more plausible explanation of their effects on blood pressure. Certain of these drugs may exert their hypotensive action by blocking the release of norepinephrine ordinarily triggered by nerve impulses at sympathetic terminals.

Early MAO inhibitors proved disappointing. Although some were powerful hypotensive agents, their severe side effects precluded their use as therapeutic agents and also aroused skepticism that MAO inhibition was a sound approach to the problem. Subsequent studies showed that the high toxicity of earlier MAO inhibitors lay primarily in their chemical derivation from hydrazine, a highly toxic compound that can cause damage to the brain and other tissues.

A recent MAO inhibitor, pargyline (Abbott), that has undergone clinical trials at NHI, is not a hydrazine derivative. The drug appears to combine high potency as a hypotensive agent with low toxicity. As a result of the excellent performance of this drug against hypertension in clinical trials at NHI and elsewhere, pargyline recently became available to the physician in general practice under the trade name Eutonyl.

Although the inhibition of monoamine oxidase per se may be unrelated to the hypotensive action of certain MAO inhibitors, this action appears to be responsible for a number of episodes of forceful heartbeat, severe headache, and hypertensive crises reported in patients receiving MAO inhibitors, usually for the treatment of depressed states. Commonly these episodes occurred after meals, and particularly after meals in which cheese had been eaten.

Recent NHI studies have established that cheese can produce a pressor response in patients treated with MAO inhibitors. Some cheese contains relatively large amounts of tyramine, a vasoactive amine normally inactivated by monoamine oxidase. Earlier studies had shown that the blood pressure response to tyramine infusions was strikingly enhanced by MAO inhibitors, apparently because they prevented the enzymatic destruction of the amine. The present studies have shown that certain cheeses, notably aged cheddar, contained enough tyramine so that the ingestion of relatively small amounts would provide sufficient tyramine to raise blood pressure in patients receiving MAO inhibitors. In two subjects, pressor responses resultant from eating only 20 grams of the cheddar (less than 1 ounce).

Probably the major source of dietary tyramine is food products derived from bacterial or other fermentation processes. Of the food products tested, only certain cheeses contained potentially dangerous quantities of tyramine. Tyramine was found in beer and wines, notably Chianti, but it appeared quite likely that MAO-inhibited patients consuming these beverages were quite likely to become high long before their blood pressure would. Still, dietary tyramine is a factor that should always be kept in mind by physicians employing MAO inhibitors in the treatment of hypertension or certain depressed states.

Thiazide diuretics, such as chlorothiazide and related compounds, are frequently used in conjunction with hypotensive agents in the treatment of hypertension. These agents appear to potentiate the blood pressure effects of many hypotensive drugs, and, in mild hypertension, thiazide diuretics used alone may suffice to control blood pressure.

The mechanisms underlying the blood pressure effects of the thiazide drugs have not been completely explained. At first, these effects were attributed primarily to the reduced blood and plasma volume resulting from increased salt and water excretion. Other evidence indicates that this is probably only one facet of the action of these drugs, especially since one of the newer thiazide derivatives, diazoxide, is antihypertensive without being diuretic, and, in fact, causes salt retention.

The current view is that thiazide drugs affect blood pressure, at least to some extent, by a direct depressant action on the smooth muscle of blood vessels. Although this decreased blood vessel responsiveness to vasoconstrictive stimuli is thought to result from drug-induced electrolyte shifts (especially the sodium to potassium ratio) in the blood vessel wall, the supporting evidence thus far is not conclusive.

CONCLUSION

The underlying cause or causes of hypertension remain obscure and the disease itself must currently be defined by carefully excluding a battery of other disorders known to raise blood pressure; yet our ignorance of the nature and causes of hypertension has not prevented the development of a variety of effective therapeutic agents. Although these drugs are aimed at a manifestation of the disease and not the disease itself, they have prolonged the lives of many thousands of victims of hypertension and have helped to make those added years far more useful and enjoyable. Further, many of these drugs are proving to be valuable probes for research into the still mysterious mechanisms by which blood pressure is controlled, and these drugs may eventually provide the clues that will enable scientists to solve the enigma of hypertension.

DIET, CHOLESTEROL, AND ATHEROSCLEROSIS

Among the fatty substances believed to be causal factors in the development of atherosclerosis and coronary heart disease, cholesterol has been undisputed "king of the hill" for more than 20 years. The findings of countless experiments in laboratory animals and of many epidemiological studies in human populations have amassed a formidable body of evidence linking elevated levels of cholesterol in the blood to the development of the artery-clogging lesions of atherosclerosis.

There is also abundant evidence that the amounts and kinds of fat in the diet are important determinants of serum cholesterol levels. In general, serum cholesterol levels tend to be pushed up by diets high in calories and total fat, with the bulk of the fat calories derived from animal sources rich in cholesterol and saturated fats. Conversely, these levels tend to be reduced by diets containing less total fat, with the bulk of these fat calories derived from vegetable or marine oils rich in unsaturated fats.

The animal studies have shown that atherosclerosis can be induced in many species of animals by dietary manipulation and other measures that lead to elevated serum cholesterol levels. In most cases, this is done by feeding the animals a diet very high in cholesterol; but it can be done with diets very high in saturated fats. The atherosclerotic lesions produced in animals by these measures often closely resemble the lesions produced by the "naturally occurring" disease in humans. In some animals, the disease has been made to progress until its lesions exhibited the same degenerative changes (fibrosis, calcification, hemorrhage, etc.) that characterize the advanced stage of the disease in humans. And some investigators have even been able to cause myocardial infarction (heart attacks) in rats by dietary manipulation.

The evidence gained from epidemiological studies among human populations has generally substantiated the evidence gained from experiments on laboratory animals. Populations subsisting on diets high in cholesterol and saturated fats usually exhibit high serum cholesterol levels and high mortality rates from heart disease. Populations such as the African Bantu, Yemenite Jews, or Japanese, who subsist on diets very low in fat (or diets in which the fat is mainly unsaturated), usually have very low serum cholesterol levels and low mortality rates from heart disease. However, when such people migrate to countries where heart disease mortality is high, and when they adopt the dietary patterns and mode of life of these countries, their serum cholesterol levels and mortality from heart disease tend to rise, increasingly reflecting those prevalent in their adopted country.

As a result of these findings, serum cholesterol levels and factors that affect them are no longer of concern only to scientists interested in lipid metabolism. Today, physicans are more and more frequently advising patients—especially middle-aged males who appear to be coronary prone—to alter their dietary patterns in order to reduce their serum cholesterol levels and, hopefully, their risk from heart disease.

WHAT IS CHOLESTEROL?

Cholesterol is a tasteless, odorless, white fatty alcohol found in all animal fats and oils, in egg yolks, and in milk and milk products. It is the most abundant sterol in animal tissues, and the only dietary sterol to be absorbed to any great extent from the digestive tract.

The cholesterol consumed in the diet comprises only a small fraction of that found in the blood. For this reason, low-cholesterol diets have usually enjoyed only very limited success against hypercholesterolemia. The major source of serum cholesterol is the liver, which manufactures cholesterol from a two-carbon building block called acetate. Since acetate arises from the metabolism of carbohydrates and proteins as well as from fat, the liver can generate cholesterol from almost any item on the menu from soup to nuts. Although the liver is the primary site of cholesterol synthesis, it also occurs to some extent in the adrenal glands and in the blood vessel wall; and it now appears that all tissues except adult brain are capable of making this sterol.

CHOLESTEROL METABOLISM

During recent years, the continuous drumfire of reports concerning the nefarious role played by cholesterol in the development of atherosclerosis has often obscured the fact that cholesterol plays a vital role in many facets of body metabolism. It is perhaps the single most important precursor of steroids. This family of compounds includes the androgens and estrogens (male and female sex hormones); adrenal cortical hormones, which are important to the regulation of salt and water metabolism and to the mobilization of metabolic fuels to sustain the body during periods of fasting, exercise, or stress; and probably many other vital hormones.

Cholesterol is also the precursor of bile acids, which play a vital role in fat absorption. Bile acids are also the major pathway for cholesterol excretion, accounting for about 80 percent of the cholesterol excreted in the feces. Most of the rest is excreted in the feces as free sterol; the kidney apparently plays only a very minor role in cholesterol excretion, if indeed it plays any role at all.

About 70 percent of the cholesterol in serum is combined with fatty acids to form cholesterol esters. Like virtually all serum lipids, cholesterol and its esters are transported by lipoproteins. Unless combined with these large fat-protein molecular complexes, cholesterol would be insoluble in body fluids.

Cholesterol and the Atherosclerotic Lesion

The manner in which cholesterol accumulates in the inner walls of blood vessels to form atherosclerotic lesions is still controversial. The filtration hypothesis holds that lipoproteins, carrying cholesterol and other serum lipids, passively penetrate the inner lining (intima) of blood vessels, become trapped in the maze of connective tissue, and gradually accumulate to form atherosclerotic deposits. Other scientists, noting that the blood vessel wall is capable of synthesizing cholesterol and other fatty substances, argue that the blood vessel may manufacture its own lesions. Current evidence favors the view that most of the lipid found in the lesion is deposited from the blood, although the blood vessel wall may synthesize enough lipid to contribute in a small way to its own degeneration.

Favoring the filtration hypothesis is evidence that, early in the development of atherosclerosis, the pattern of lipids found in the lesions is strikingly similar to that of the blood. The lesions contain phospholipids and triglycerides as well as cholesterol, and in about the same proportions as are found in the blood. Later on, however, cholesterol becomes the dominant lipid of the lesion. It now appears that the laying down of atherosclerotic lesions is a dynamic process. Although lipids are continuously entering and leaving the blood vessel wall, the lesion is built up because the net rate of entry exceeds the net rate of departure. Cholesterol may accumulate in the lesion to a greater extent than do triglycerides or phospholipids because its turnover rate is slower than that of the other lipids.

Also supporting the filtration hypothesis is the abundant evidence that hypertension hastens the development of atherosclerosis; that atherosclerotic lesions are uncommon in low-pressure vessels such as the pulmonary arteries; and that lesions tend to develop earliest at arterial branching points, where eddy currents, pressure differentials, or pulsation differences might favor the passive penetration of the intima by serum lipoproteins.

Cholesterol and other serum lipids also show a strong predilection to deposit at sites where the blood vessel wall has been injured. Animal studies indicate that, once laid down, the lesion may serve as a rallying point for the deposition of further lipid; and so the lesion may continue to progress even in the absence of elevated serum lipid levels.

THERAPEUTIC APPROACHES TO HYPERCHOLESTEROLEMIA

The strong association between elevated serum cholesterol levels and increased susceptibility to atherosclerosis and coronary heart disease has spurred research seeking safe, effective, and practical means for bringing high serum cholesterol levels down to normal. What are "normal" serum cholesterol levels? Nobody is sure, but most investigators agree that the levels considered normal in Americans are probably too high.

A recent study at NIH yielded the following values for serum cholesterol as representing the upper limits of normal for Americans. Values higher than these are "quite probably abnormal." Values are expressed in milligrams of cholesterol per 100 milliliters of serum.

Age	*Total cholesterol*
Males:	
0 to 20	230
21 to 55	[1] 230
55 and up	370
Females:	
0 to 25	240
26 to 60	[2] 240
60 and up	380

[1] Plus 4 (age −20).

[2] Plus 4 (age −25).

How low should serum cholesterol levels be pushed? Again, nobody is sure, but many investigators are inclined to believe that the lower the serum cholesterol, the better. Theoretically it is possible to drive serum cholesterol levels down so far that health might be endangered. However, given the serum cholesterol levels of most Americans and the limitations of currently available techniques for lowering serum cholesterol, this is not likely to pose much of a problem.

Diet.—The most widely used therapeutic approach to hypercholesterolemia has been dietary modifications. For a time, dietary cholesterol was believed to be the major offender in hypercholesterolemia; but low-cholesterol or no-cholesterol diets were only moderately effective in some patients, completely ineffective in many others. It was subsequently shown that most of the cholesterol of serum is synthesized by the liver, and that in many instances this organ could turn out enough cholesterol to overload the system even when the diet contained no sterol of any kind. In some cases, the liver can even produce hypercholesterolemia in subjects on fat-free diets, provided that these diets contain excessive amounts of carbohydrate.

Greater success has attended the use of diets low in total fat, most of which is polyunsaturated fat derived from vegetable or marine sources. There appears to be a direct relationship between the degree of unsaturation of any given fat and its effects on serum cholesterol: the more unsaturated the fat, the more it reduces serum cholesterol levels. Serum cholesterol levels have been dramatically reduced by diets containing more than 40 percent of their calories as fat, provided that this fat was unsaturated.

The mechanism by which unsaturated fats work their magic has not been conclusively established. They do not reduce the rate of cholesterol synthesis; in fact, they appear to increase it. However, current evidence suggests that unsaturated fats cause an even sharper increase in the production and excretion of bile acids, and thus cause a net loss of cholesterol by the body.

Unsaturated fats are generally ineffective in reducing serum cholesterol when added to a diet high in saturated fat. They must largely replace saturated fats; and, in some therapeutic diets, the delicate balance between saturated and unsaturated fats provides little leeway for cheating. One such diet has brought about a 15-percent reduction in serum cholesterol until a small quantity of saturated fat was added. Although this additional saturated fat comprised only 1 percent of the total fat calories of the diet, it completely abolished the diet's cholesterol-lowering effect.

Diet and heart disease feasibility study.—Epidemiological studies indicate that most Americans habitually consume a diet hardly calculated to protect them against atherosclerosis: it is high in calories, total fat, and saturated fat. Many scientists feel that this diet is largely responsible for our present appalling mortality from heart disease. They believe that heart disease mortality might be substantially reduced by modifying this diet. They contend that these modifications (which entail a substantial reduction in total dietary fat and the liberal substitution of unsaturated for saturated fat) need not cause any major upheaval in prevailing dietary habits nor make eating any less enjoyable.

In support of this contention, several limited, short-term studies on small population groups have shown the proposed type of diet to be generally effective in reducing serum cholesterol levels, simple enough to be prepared in the average kitchen, and palatable enough to encourage the great majority of subjects to follow it faithfully throughout the period of study.

Still to be proved, however, is whether large numbers of Americans will voluntarily accept any basic modification in dietary habits for prolonged periods; and, if so, whether such modifications will appreciably affect their presently better-than-even chances of dying from cardiovascular disease. To obtain such proof will require long-term population studies on a scale never before attempted.

Before such an ambitious project can be undertaken with any great prospect of success, its feasibility must be carefully tested. This is currently being done by means of a series of 6 studies involving about 1,500 healthy, married male volunteers between the ages of 45 and 64.

The participants volunteer for an initial 13 months of dietary modification. This entails slight to moderate changes in the amount and type of dietary fat and the amount of dietary cholesterol, but no drastic changes in food and eating patterns. To effect these modifications, the participants are asked to purchase special, fat-containing foods from diet-heart study food centers, set up especially for the study. Other foods are purchased on the open market.

Although these foods require special methods of processing that usually increase their cost, study participants can obtain them at prices commensurate with those of similar nonprocessed foodstuffs. The difference is paid by the study. The food industries, who have given splendid assistance to the study, are attempting to hold these food costs to a minimum.

Each participant visits the diet-heart research center monthly at first, then at bimonthly intervals. At each visit nutritional and medical history, pulse, blood pressure, weight, serum cholesterol determinations, and other biochemical data are recorded.

Research grant awards for the study were made in June 1962. The necessary mechanisms and arrangements have been established, the recruitment of volunteers completed, materials for the instruction and guidance of participants prepared, and the dietary modification phase begun. The study thus appears to be well launched upon its course. This has been made possible by the cooperation, consultation, and participation of many people, agencies, and institutions. As the collaborating investigators state: "With the cooperation of heart associations, medical societies, individual physicians and scientists, the food industry, and a variety of other public-spirited individuals and groups, every possibility exists for the achievement of success in this important study in the expanding effort to control today's No. 1 epidemic disease, atherosclerotic coronary heart disease."

Although successful in treating many cases of hypercholesterolemia, diet therapy has been ineffective often enough to stimulate the search for drugs that might lower serum cholesterol levels by some direct action on processes involved in the absorption, synethesis, transport, or excretion of cholesterol.

Agents that inhibit cholersterol absorption.—Beta sitosterol and several other plant sterols have been found to reduce the absorption of cholesterol from the digestive tract. These sterols apparently work by competing with cholesterol for the mechanisms involved in the transport of cholesterol across the intestinal wall. However, the therapeutic value of such compounds, like that of low-cholesterol diets, is limited by the fact that dietary cholesterol is a relatively unimportant source of serum cholersterol.

Agents that inhibit cholesterol synthesis.—Inasmuch as the liver has been shown to manufacture most of the cholesterol found in serum, the current surge of interest in compounds able to block cholesterol synthesis is hardly surprising. Although beautifully direct, this approach is nevertheless beset by formidable problems. One of them is to determine which, if any, of the biochemical steps involved in cholesterol synthesis can be blocked safely. Theoretically, cholesterol production might be blocked at any of a number of biochemical steps. However, many of the compounds evolved during cholesterol synthesis are also needed for the synthesis of other substances vital to the body. Thus blockade of steps occurring too early in cholesterol synthesis might also seriously compromise the synthesis of fatty acids, steroids, hormones, and other vital metabolities; blockade of very late steps might lead to the accumulation of foreign sterols possibly more atherogenic than cholesterol.

A compound called delta-4-cholestenone is an example of a drug that blocked a step too early in cholesterol synthesis. In animals, the compound was highly effective in blocking cholesterol synthesis and in reducing serum cholesterol levels. Unfortunately, it was almost equally effective at blocking the production of vital adrenal steroids, leading to massive hypertrophy of the adrenal glands and to other distressing effects. To round out a generally dismal picture, the fall in serum cholesterol brought about by delta-4-cholestenone was accompanied by a striking increase in serum levels of a compound called dihydrocholesterol. This compound proved unable to perform any of the useful purposes of cholesterol, but substituted admirably for the latter in the formation of atherosclerotic lesions.

Triparanol (Merrill), a drug that had apparently avoided the precursor problem, ran head on into another. The compound blocks a very late step in cholesterol production, and the resulting fall in serum cholesterol is accompanied by a rise in serum levels of desmosterol. Desmosterol is identical to cholesterol except for two missing hydrogen atoms. This close structural similarity aroused the suspicion that desmosterol would behave very much like cholesterol in the body. The suspicion was confirmed by findings showing that desmosterol substituted readily for cholesterol in the production of steroids, sex hormones, bile acids—and atherosclerotic lesions.

Although the drug appeared to be nontoxic in most patients, it produced severe side effects in some. These included dry, scaly skin, hair loss, changes in hair color, and corneal cataracts. As a result, the drug has been withdrawn from the market. Scientists are currently seeking the reasons for these side effects, hoping that such knowledge will prove valuable in the development and assessment of future anticholesterolemic drugs.

An enzyme preparation called hepatocatalase, obtained from beef liver, has been found to inhibit cholesterol synthesis and to reduce serum cholesterol levels in animals and in humans receiving it by muscular injection. Recent studies by NHI grantees indicate that the inhibition of cholesterol synthesis by the preparation does not result from hepatocatalase itself, but rather from a peptide also present in the preparation. The scientists have succeeded in isolating the active inhibitor, a peptide of relatively low molecular weight. They feel it may be possible to synthesize this peptide, once its structure has been worked out, and that the peptide is unlikely to produce anaphylactic or immuological reactions in the body (although no evidence of toxicity has been reported for the enzyme preparation either).

Nicotinic acid (niacin) is an inhibitor of cholesterol synthesis that appears to combine clinical effectiveness with low toxicity. The drug does produce side effects in some patients—flushing, gastrointestinal disturbances, increased pigmentation of the skin—but these are seldom serious enough to necessitate discontinuing use of the drug. It also causes minor abnormalities of liver function, but no signs of liver damage; and the abnormalities promptly revert to normal when treatment is discontinued. Used alone, nicotinic acid is generally effective in bringing about moderate reductions in serum cholesterol. It is even more effective when used in conjuction with cholesterol-reducing diets.

NHI grantees report that a new compound called CPIB ester (Ayerst) produced an excellent, sustained reduction of serum cholesterol and other serum lipids in limited clinical trials in 41 patients. The drug was well tolerated, and careful studies revealed no evidence of toxicity. There was also no evidence that the fall in serum cholesterol produced by the drug was accompanied by any increase in serum levels of other sterols.

For unknown reasons, in patients receiving warfarin, CPIB ester appeared to augment the action of the anticoagulant, necessitating reduced warfarin dosage; however, CPIB ester produced no bleeding tendency in subjects not receiving warfarin. Again, for unknown reasons, CPIB ester was considerably more effective in females than in males. Among 27 women treated with CPIB ester, serum cholesterols fell by an average of 25 percent, serum phospholipids by 17 percent, and serum triglycerides by 42 percent. Among 14 males, serum cholesterols fell by 12 percent, serum phospholipids by 9 percent, and serum triglycerides by 30 percent.

The mechanism by which CPIB ester lowers serum lipid levels is still unknown. The grantees feel that further clinical trials of the compound are indicated to clarify its possible role in the prevention and treatment of atherosclerosis.

Agents that affect cholesterol excretion.—A number of hormones and drugs appear to lower serum cholesterol by stepping up the rate of cholesterol excretion relative to the rate of synthesis. Among these agents, thyroid hormones have been most intensively studied.

For many years, it has been known that serum cholesterol levels tend to be unusually low in hyperthyroid subjects and high in subjects with hypothyroidism due to myxedema or other thyroid disorders. Not surprisingly, numerous attempts have been made to employ thyroid hormones in the treatment of patients with hypercholesterolemia.

Thyroid hormones are effective against hypercholesterolemia, but the doses required to elicit the cholesterol-lowering action of the hormone also frequently raise metabolic rates; cause nervousness, tremors, and other signs of hyperthyroidism; and very often cause angina pain in patients with ischemic heart disease. Angina pain often occurs even in patients receiving thyroid hormones in doses too small to produce any demonstrable signs of hypermetabolism.

A number of scientists have been seeking means of modifying the chemical structure of thyroid hormones to produce an analog that will retain the cholesterol-lowering properties of the natural hormone, but fewer of the other metabolic effects. Thus far, the attempts to chemically tame these rambunctious hormones have achieved only limited success.

Estrogens.—The fact that women enjoy a considerably greater degree of protection against coronary heart disease than do men has been known for years. Data from the Framingham study indicate that not only do women develop heart disease some 10 to 20 years later in life than do men, but they also tend to develop less lethal forms of the disease (e.g., angina pectoris rather than myocardial infarction). This protection appears to reside in the estrogens secreted by the endocrine glands of women during their reproductive years. In turn, the protection conferred by estrogens appears to stem from their effects on serum lipid patterns, especially the distribution of cholesterol and other serum lipids among the serum lipoprotein classes.

Lipoproteins are divided somewhat arbitrarily into two weight classes: high-density and low-density lipoproteins. In man, the low-density fraction transports most of the cholesterol and neutral fat (triglycerides) of serum. A decided preponderance of low-density lipoproteins is associated with elevated serum cholesterol levels and with increased susceptibility to atherosclerosis. By some still-mysterious action, estrogens increase the relative amounts of cholesterol and other lipids carried by the nonatherogenic high-density lipoproteins.

Many scientists have explored the use of estrogens to confer their "protection" on postmenopausal women and upon middle-aged males who were coronary-prone or who had already suffered heart atacks. For the most part, these were short-term studies yielding inconclusive, often conflicting results. In many of these, the protection (if any) conferred by estrogens seemed meager in view of the side effects frequently produced by therapy: breast enlargement and loss of sexual drive in males and uterine bleeding in women.

A more recent long-term study conducted among middle-aged males indicates that, while some degree of breast enlargement and loss of libido may occur with estrogen therapy, this price is not excessive in view of the protection afforded by these hormones. And another long-term study suggests that estrogens may confer significant protection against heart disease in doses that cause no appreciable feminizing effects and no deleterious effects upon libido.

The subjects of the former were middle-aged males who had previously suffered at least one heart attack. Half received conjugated equine estrogens; the others received a placebo. The estrogen-treated group received 10-milligram daily doses, the dosage required to produce the so-called "beneficial" serum lipid pattern: e.g., an elevation of serum high-density lipoproteins and a reduction in the cholesterol-phospholipid ratio.

This dosage usually produced feminizing side effects, but few other complications. Apparently these were enough for many patients; the dropout rate was 40 percent in the estrogen-treated group versus 30 percent in the control group. An unexpected early finding was a high percentage of recurrent attacks in subjects receiving high doses of estrogens within 3 months after a heart attack. From this experience, the grantees concluded that it is unwise to start estrogen therapy until at least 3 months after acute heart attacks, and that initial dosage should be low, gradually working up to therapeutic levels. In retrospect, they also feel that the 10 milligrams of estrogens per day used in this study might have been a little high, and that more than 5 milligrams per day is probably unnecessary.

Still, the results achieved with the regimen were gratifying. Recurrent heart attacks were sharply reduced, and the 5-year mortality rate in the estrogen-treated group averaged 50 percent lower than in the controls. Especially gratifying were the results obtained with "good risk" patients: those having first heart attacks. The 5-year mortality in this group was only 6 or 7 percent versus the usual 15 to 20 percent.

The results of the other long-term study suggest that estrogens may confer protection against heart disease in doses that exert no striking effects on serum lipids, and—more important—no appreciable feminizing effects and no deleterious effects on libido. This study, too, was carried out among middle-aged males who had previously suffered heart attacks. In the estrogen-treated group, dosage was adjusted on an individual basis: low initial doses were gradually increased until the patient noted slight breast tenderness. He was subsequently maintained on this dosage unless increased side effects necessitated reducing it.

Over the 5-year period of this study, the therapy caused no untoward clinical effects, and adverse effects on sexual drive were infrequent. The dropout rate in this study was an extremely low 3 percent.

Three estrogen preparations were evaluated. Only one, consisting of conjugated equine estrogens, appreciably affected 5-year survival, however, this preparation performed impressively. During the first 18 months, mortality in the group receiving this preparation was less than half that of the placebo group. Thereafter, the effects were less spectacular, but were still substantial. After 3 years, the mortality in this group was still one-third lower than in the placebo group.

A surprising finding was that, in the dosages used, conjugated equine estrogens decreased mortality, but produced no significant changes in serum lipid patterns. Conversely, the other preparations evaluated (chemically pure, synthetic estrogen compounds) produced the so-called "beneficial" serum lipid pattern, but had no effect whatever on long-term survival. The grantees conclude from these observations that the antiatherogenic effect of estrogens may reside in some unknown action rather than in that affecting serum lipoprotein patterns.

These studies suggest that middle-aged males with overt coronary heart disease and perhaps those who are cornorary-prone might benefit substantially from estrogen therapy. Further, the protection conferred by these hormones need not necessarily entail intolerable side effects. Although these findings do not settle the controversy surrounding the use of estrogens as therapeutic or prophylactic measures against coronary heart disease, they indicate that this line of attack is promising enough to merit more extensive scientific evaluation.

CONCLUSION

The feasibility of reducing serum cholesterol levels by dietary manipulation, drugs, and certain hormones has been demonstrated. The techniques have been tested, and they work. However, none of them are effective in all cases, nor are any of them as effective as one might wish.

This approach to the prevention of heart disease is relatively new. It may well turn out to be only another blind alley, since it remains to be proved that reducing serum cholesterol levels will be of any benefit in reducing heart-disease mortality. However, it appears to be the most promising line of attack currently available, and so it will be pursued. If medical research confined its attention only to sure things, there would be no medical research.

ARTIFICIAL HEARTS

Each year many thousands of Americans perish because a hopelessly diseased or injured heart has failed to function in an otherwise reasonably sound and healthy body. At present, nothing can be done to salvage these lives because there are no replacements for hearts damaged beyond repair. However, 10 years from now—and some say 3 years from now—this may no longer be the case.

The proven practicality of blood pumps for heart-lung machines and of artificial blood vessels, valves, and other substitute parts for the living heart has led many scientists to believe that small, mechanical blood pumps may be designed for installation within the body. Some of these scientists have been concerned with the development of single-chambered pumps to serve as auxiliary or "booster" hearts, their goal being to assist, rather than to replace, a failing heart. Others envision a prosthetic heart—complete with inflow and outflow tracts, valves, pumping chambers, and power source—for the total and permanent replacement of irreparably damaged human hearts.

Research toward this goal is underway in at least 13 research institutions, most of it with NHI grant support. To date, no fewer than 17 types of artificial hearts have undergone preliminary trials in animals, and others are in earlier stages of development. As yet, none of these devices is considered sufficiently developed for installation in humans; however, scientists working on the problem predict that hearts will be artificially replaced in humans within 10 years, and possibly within 3 years.

"BOOSTER HEARTS"

Several single-chambered blood pumps have been designed to provide pumping assistance to overburdened or failing hearts. The object is to reduce the workload of the heart while maintaining systemic blood pressure and flow at adequate levels.

One such pump, recently, tested successfully in animals, consists of a silastic bulb with Teflon cuffs housed in a rigid plastic chamber. The pump is installed so as to bypass the aortic arch: the inflow line takes up blood from the ascending aorta just above the origin of the coronary arteries, and the outflow line discharges into the descending aorta.

The pump is driven by bursts of compressed air generated outside the body and transmitted by a tube through the chest wall. In operation, the sequence of events is as follows: (1) The left ventricle contracts, filling the silastic bulb of the booster pump. (2) As the left ventricle relaxes and the aortic valve closes, the R wave of an electrocardiograph triggers a solenoid valve. (3) The valve releases a burst of compressed air to propel the blood in the bulb forward while the ventricle is refilling with blood.

This action of the booster pump maintains systemic blood pressure, but leaves in its wake a low pressure at the aortic valve. Thus, during its subsequent contractions, the left ventricle will be ejecting blood against a lower resistance. Animal experiments indicated that this resulted in a substantial reduction in left ventricular work.

The booster pump apparently inflicted very little damage on blood cells and caused no blood clots, even though the animals were receiving no anticoagulants. When the pump was stopped, there was an initial fall in blood pressure, but it quickly returned to normal levels and remained there. Thus, when the pump and implantation technique are perfected, it may become possible to install the pump to render circulatory support during crises such as heart attacks or heart failure, after which the pump could be left in place to provide future assistance as needed.

A booster pump of a similar type was installed in a patient who was in extremis from left ventricular failure that had failed to respond to all other methods of therapy. The pump took over the function of the failing left ventricle and performed successfully for 4 days, but was unable to save the patient's life. This air-driven, electronically controlled pump took up blood from the left atrium and pumped it directly into the descending aorta, bypassing both the left ventricle and the aortic arch.

SOME PROTOTYPE ARTIFICIAL HEARTS

Artificial hearts currently under development operate in much the same way as the living heart, by alternately squeezing and relaxing blood-filled chambers. The living heart has two such chambers, called ventricles, which are its main pumping chambers. Two subsidiary compartments, or atria, serve as collecting chambers that pump blood into the ventricles.

Since most mechanical hearts are designed for the complete replacement of the living heart, they contain two separate pumping chambers. One sends "used" venous blood to the lungs where it is purified of waste gases and oxygenated; the other receives the oxygenated blood and pumps it to all parts of the body. One-way valves control the direction of blood flow, as in the living heart.

Though artificial hearts and living hearts operate on the same general principle, they differ markedly in the application of this principle. Thus, chambers of the living heart are surrounded by spirally wound bands of muscle which alternately contract and relax to effect a pumping action. Blood chambers of artificial hearts, however, are compressed by various mechanical systems instead of by muscles.

Pneumatic or hydraulic systems power several experimental mechanical hearts. In these hearts elastic blood chambers are encased in a rigid outer shell of metal or plastic. The elastic chambers collapse and expand in response to cyclic variations in either gas (pneumatic) or fluid (hydraulic) pressure between the inner chambers and their rigid housing. The pressure variations, in turn, are caused by a pulsating flow of gas or fluid generated by devices outside the body and transmitted to the artificial heart by a tube through the chest wall. Since this type causes the least damage to blood cells, this family of pumps includes several of the most promising artificial hearts. The elastic chambers may be either sac- or tube-shaped, or they may have a flat diaphragm or membrane as the sole elastic component of an otherwise rigid pumping chamber.

Piston-driven blood pumps permit easier calibration of the volume of blood ejected with each pumping stroke; however, their usefulness had been limited because of the excessive destruction of blood cells trapped between the piston and cylinder wall. Several new pumps of this type use a piston considerably smaller than the cylinder. Acting as a seal between piston and cylinder is a "rolling diaphragm" of Silastic and Dacron mesh that practically eliminates damage to blood cells. Thus, these pumps combine the advantages of a reciprocating piston with the gentle blood-handling characteristics of an elastic membrane.

In one type of rolling diaphragm pump, the piston is driven by bursts of air from an external source. In another type a cam, driven back and forth by a tiny direct-current electric motor, imparts a pumping action to the piston and rolling diaphragm. The assembled unit—pumping chamber and motor—is sheathed in a fluid-tight plastic capsule and plastic-coated wires connect the electric motor to an externally located power source.

Insulated wires also supply power to an artificial heart which contains five electromagnets or solenoids. The charging and discharging electromagnets move synchronously back and forth to regulate valve action and compress blood chambers. The chambers are permanently bathed in oil so that generated heat may be readily dissipated.

At least two other prototype prosthetic hearts contain electric motors—a pendulum-type pump and a roller-type pump. In one of these, a motor suspended on pivots (the "pendulum") swings back and forth within a rigid outer housing, alternately compressing each centricle against the housing. To-and-fro excursions of the motor-pendulum are caused by an eccentrically mounted level which connects the motor shaft to the outer housing. The roller pump employs a small, motor-driven roller to compress the ventricles. Polyurethane foam inserted between the ventricles and housing provides a yielding surface which minimizes damage to red blood cells.

VALVES

A variety of valve types are used in artificial hearts to maintain unidirectional blood flow. One type of artificial valve simulates the living heart's aortic valve. It consists of three adjoining pockets, or cusps, of flexible plastic which readily collapse under the pressure of forward-flowing blood, but billow out to close the opening as forward flow ceases. Other valves that close, or seat, under the pressure of backward-flowing blood are simple flap and ball valves.

POWER SOURCES

All artificial hearts are powered externally, most of them via tubes or wires that penetrate the chest wall. It is believed that, with existing technology, methods of this kind allow greater control of heart rate, output, and other aspects of heart performance while minimizing the risk of mechanical failure. A notable exception is a method, reported by grantees at the University of Missouri, that eliminates the need for wires or tubes but retains the present control-advantages of an externally located power source. According to their method, the heart is powered remotely by an electromagnetic field generated by a coil outside the chest wall. The magnetic field induces a voltage into a similar coil buried within the chest, which then supplies energy to an artificial internal heart. Although artificial hearts have not as yet been driven with this system, the scientists' animal experiments demonstrated that up to 50 watts could be transmitted through the chest wall with no apparent discomfort to the animal and without appreciable temperature rise in the coils or tissue. This is more than enough power to drive a mechanical heart.

In the future, after externally powered hearts have proven their worth in patients, totally implantable power sources may become feasible. These may take the form of long-life batteries, thermoelectric devices that convert body heat into electricity, or piezoelectric devices that convert motion (such as the heaving motion of the rib cage during respiration) into electrical energy. A small, implantable nuclear powerplant may even become feasible in the not too distant future.

REGULATING THE PERFORMANCE OF ARTIFICAL HEARTS

A successful prosthetic heart must do more than merely maintain simultaneous and unidirectional flow through the pulmonary and systemic circuits, and perform this dual task with minimal trauma to fragile blood elements; it must also be capable of varying its performance to accord with the body's ever-changing circulatory requirements. And, although the amount and pressure of blood ejected by each ventricle may vary from one pumping stroke to the next, the total volume of blood pumped by one side of the heart must equal that of the other side over a period of several hours, lest one circuit become engorged and the other ischemic.

That most nearly perfect pump, the living heart, is controlled by a number of nervous and hormonal mechanisms that effect appropriate changes in blood flows and pressures by altering the rate, force, and duration of heart contractions and the calibers of blood vessels. In varying degrees, depending upon the type of mechanical pump used, the performance of artificial hearts can also be monitored and altered from moment to moment to meet physiological exigencies. An important question was what physiological parameter or parameters should the pump be "geared" to. Since an artificial heart (or any pump, for that matter) can pump only as much fluid as it receives, investigators proceeded on the working hypothesis that pump regulatory mechanisms should be based on venous return or filling. This is especially important in pumps that have a fixed stroke volume because, in the event of low venous flow, such pumps create a partial vacuum or suction that can cause collapse of the great veins, air embolism, or inversion of flexible pistons and valves.

To overcome this problem, NHI grantees at the University of Pennsylvania developed electronic control apparatus that translates venous pressure variations into variations of stroke rate by an artificial ventricle. In their control system, variations in venous pressure are converted into voltage of varying intensity and fed into components of a servomechanism. If the voltage (representing pressure) is different from a preset reference value, the mechanism effects an appropriate change in the voltage supplied to the ventricle, and thus its rate.

Tests of the servomechanism in a mock circulatory system demonstrated its ability to maintain a constant venous pressure over a wide range of flow rates by changing the stroke rate of a small artificial ventricle. In animal experiments, in which the ventricle and control apparatus were used to maintain total right heart bypass in anesthetized dogs, the system responded well and successfully compensated for various procedures designed to alter venous pressure. These procedures included temporary occlusion of the great veins, infusion of saline solution, and injections of various drugs.

A second model of the control apparatus has been constructed entirely of transistors and other solid state components. "It will be easy to proceed from this step to further miniaturization should implantation of the control apparatus later seem desirable," the grantees reported. They speculated that the apparatus could be miniaturized to the size of a pea, and implanted in the ventricle wall.

An antivacuum bellows system, devised by NHI grantees at the Cleveland Clinic Foundation for an air-driven heart, prevents excessive ventricular suction and tends to equalize the outputs of both ventricles. As described previously, the elastic ventricle is encased in a rigid housing into which air is alternately pumped and withdrawn by an externally located pump. On one side of the ventricle is an air space. This air space is entirely separated from the driving gas but is connected through small holes in the rigid housing to a distensible bellows or balloon outside the housing. Air from the balloon, responding to negative pressure during the heart's filling phase, enters the housing and exerts enough counterpressure on the expanding ventricle to negate excessive suction and thus prevent collapse of the atria and great veins. In other words, the suction is exerted preferentially on the balloon rather than on the atria and veins. Thus, venous inflow is not interrupted during the suction phase and adequate ventricular filling, hence output, occurs, with equilibration of the outputs of both ventricles.

Hearts equipped with this simple, effective bellows system and driven by a reciprocating air pump were easily inserted in the chests of dogs. And, although the dogs were maintained by these early sac hearts for up to 21 hours, two major problems barred long-term survival. Firstly, increased resistance (constriction) in peripheral arteries led to pooling of blood in the spleen and venous system, and consequently to a critical reduction in heart output. This arterial reaction was attributed to the high-peaked pressure waves generated by the reciprocating pump. When used to drive the heart in a mock circulatory system, this nonphysiologic waveform of pumping action caused the heart to jump up and down on the table. The vigorous motion posed an additional threat to long-term studies, as it could conceivably cause rupturing of arterial and venous connections to the heart. For help in combating this problem, the grantees obtained the services of NASA engineer, Kirby W. Hiller, who developed a more flexible self-regulating control mechanism based on feedback principles. This system, incorporating a NASA variable waveform generating device, can be preprogramed to generate any physiological wave desired. It also monitors flows, pressures, and the position of the moving ventricular walls and, using this information, develops instructions for and effects changes in the waveform's amplitude, rate, and pressure levels to maintain a physiological balance of these functions. The variable waveform pressure generator consists essentially of an electronically controlled valve that controls two variable area orifices, one to the high pressure supply and one to the low pressure supply. With this system, programed to produce a physiological pressure wave roughly in the shape of a small "h," the heart beat smoothly.

Blood clot formation and embolization is the second and most serious obstacle to long-term in vivo studies of the artificial heart. Dogs that survive longer than 12 hours almost invariably succumb to brain damage caused by multiple embolization. This was attributed to the material (polyurethane) used in constructing earlier sac-type hearts and also to the inherently greater clotting tendency of dog blood. For these reasons, calves are being used as experimental subjects for hearts constructed of silastic-impregnated dacron mesh. Successful long-term clinical results of prosthetic mitral valves augurs well for these changes; the same kind of valves almost invariably thrombosed (clotted) during earlier tests in dogs.

Clinical trial of the silastic sac heart awaits only long-term success in calves, according to the grantees. These experiments are now in progress and, unless further problems arise. selection of patients and clinical trials will commence within 3 years, they predict.

CONGENITAL HEART DISEASE

Congenital heart disease is an old enemy; most of its manifestations had been cataloged in the first quarter of this century, not only in cadavers but in living patients as well. This knowledge, however, was largely academic, for little or no help could be offered to an infant afflicted with an inborn heart defect. Death in early infancy was the expected and usual outcome, although some patients lived into early adulthood as partial or total invalids.

In all, there are 35 recognized types of congenital malformations. These defects, occurring singly or in combination, include: Abnormal vascular rings which constrict the esophagus or trachea; constriction, or coarctation, of the aorta; patent ductus arteriosus, a blood channel that normally closes soon after birth; narrowed, or stenosed, heart valves and outflow tracts; abnormal openings in the muscular partitions between heart chambers; transposition of the great vessels; single ventricle; and others.

As recently as 1944, only 2 of the 15 most common forms of congenital heart disease could be corrected, and 2 additional types alleviated, by surgery. Today, corrective or palliative operations are available for all of the common defects and most of the rarer forms as well.

15 most common forms of congenital heart disease

Cardiovascular defect	Defect either palliated or totally corrected through surgery	
	1944	1964
1. Patent ductus arteriosus	Corrected	Corrected.
2. Vascular ring	do	Do.
3. Coarctation of the aorta	No	Do.
4. Aorticopulmonary window	do	Do.
5. Atrial septal defect	do	Do.
6. Atrioventricularis communis	do	Do.
7. Anomalous pulmonary venous drainage	do	Do.
8. Ventricular septal defect	do	Do.
9. Transposition of the great vessels	do	Corrected and palliated.
10. Tetralogy of Fallot	Palliated	Do.
11. Taussig-Bing heart	No	Palliated.
12. Pulmonic and infundibular stenosis	Palliated	Corrected.
13. Aortic and subaortic stenosis	No	Do.
14. Tricuspid atresia	do	Palliated.
15. Single ventricle	do	Do.

Various studies suggest that most congenital defects are usually developmental abnormalities caused by virus infections, vitamin deficiencies or excesses, exposure to radiation, lack of tissue oxygen, or other factors affecting the fetus at critical stages in its development. Only rarely are these defects genetically transmitted. Further investigations into the causes of congenital heart disease may ultimately enable physicians to prevent these defects. In the meantime, however, remedial surgery is our main weapon, and one that is being wielded with spectacular results: of the estimated 50,000 children born in the United States with congenital heart defects each year, about 80 percent of them can now be cured or helped by surgery.

This spectacular progress in heart surgery began in the 1940's and early 1950's with the development of ingenious techniques for repairing some of the simpler defects. However, initial progress was slow, and the surgeon had to work by feel alone in an operative field that squirmed and pulsated with each heartbeat.

Before they could undertake the correction of any but the simplest heart defects, surgeons had to learn how to sustain life during direct-vision surgery in widely opened, stilled hearts. The development of two such life-support techniques, hypothermia and extracorporeal circulation, has not only made such surgery possible, but has also paced most of the progress in this field.

Hypothermia, or body cooling, slows body metabolism and reduces tissue oxygen requirements so that the heart and brain can tolerate short periods of interrupted bloodflow (6 to 8 minutes). For longer periods, surgeons turned to extracorporeal circulation. In this technique, blood bypasses the heart and lungs completely. It is pumped and oxygenated by a heart-lung machine located outside the body. Once hypothermia and extracorporeal circulation had demonstrated their individual worth in cardiovascular surgery, surgeons capitalized on the advantages of both. This combination at last provided the surgeon with direct-vision access to the stilled heart for periods long enough (up to 7 hours) to correct even the most complicated defects.

Although several types of heart-lung machines are available for clinical use, all are adequate for most cardiovascular surgery. The type of machine employed is considerably less important than the surgeon's skill and familiarity with the equipment in determining the success or failure of an open-heart operation.

This is not to say that developmental work on these and related machines is ceasing or even slowing down; this is far from the case. Indeed, recent developments in instrumentation are not only increasing the safety of existing operations and of known life-support techniques, but are also expanding horizons in these fields, adding new techniques to an already impressive repertoire. Of equal importance, these developments are extending the benefits of modern heart surgery to patients who, because of such diverse factors as age, economics, accident, or conflicting religious belief, formerly could not qualify to receive them.

For example, physicians are now scheduling remedial heart operations for more newborn infants than ever before, instead of recommending that a child live with his defect for several years before surgery is performed. This is because, in cases not treated by surgery, about 34 percent die during the first month of life and 61 percent within the first year. Many of these infants can be saved, according to findings by a group of NHI grant-aided surgeons in Houston, Tex. The surgeons, headed by Dr. D. A. Cooley, recently reported on 400 consecutive operations they performed since 1954 on infants less than 2 years old. Sixty percent of these infants were less than 3 months of age.

The operations were performed by a wide variety of congenital defects; the most common lesions, accounting for 292 of the 400 cases, were patent ductus arteriosus, transposition of the great vessels, ventricular septal defects, and coarctation of the aorta.

The overall survival rate was 72 percent, or 288 of the 400 patients. Mortality varied with the complexity of the malformation, and was highest in patients with multiple anomalies.

During the period of this study, autopsies performed on 154 infants with congenital heart defects and who were not treated surgically, showed that defects in 70 of these patients were amenable to palliation or correction through surgery.

The high salvage rate is surgically treated patients and the high incidence of death in untreated similar cases "emphasizes the need for an even more aggressive effort toward early diagnosis and proper treatment in these cases in our own hospital," the grantees conclude.

Other grantees, in Boston, achieved dramatic increases in the blood oxygen levels of severely cyanotic infants ("blue babies") by placing them in a compression chamber and administering 100 percent oxygen at pressures of 3 to 3.6 atmospheres absolute. Although the improved oxygenation was temporary (upon decompression, it falls promptly to precompression levels), it enabled four of these critically ill infants to better withstand palliative heart surgery which was performed inside the capacious, 29- by 8-foot pressure chamber. Three of the infants survived and were greatly improved. Although this method, called hyperbaric oxygenation, is used with extracorporeal circulation and hypothermia, it actually constitutes a third and new life-support technique of high potential in the cardiovascular field and other areas as well.

With so many newborn (even premature) infants undergoing heart surgery, a computer method of analyzing fetal electrocardiograms is a particularly timely development. Such analyses are complicated because the inherently weak fetal heart signals must be distinguished from the mothers' ECG signals and from other extraneous signals. NHI grantees at Georgetown University Medical

School have used a digital computer to process such signals. Once a fetal electrocardiogram has been digitalized, it can be processed and manipulated in many ways. Some of these operations verify the presence of a fetal signal, establish its rate, help to reconstruct the waveform, or provide statistical parameters about the signal itself. In this way, it is possible to analyze a baby's heartbeat before birth, thus giving the physician a forecast of possible congenital problems.

The procurement of the largest quantities of fresh blood ordinarily needed to prime the heart-lung machine has frequently posed problems in scheduling open-heart operations. A method recently reported by NHI grantees completely liminates the need for blood to prime the machine; a 5-percent solution of dextrose is used instead. Perfusion is carried out under normothermic conditions, using a disposable plastic oxygenator. The method is convenient, increasing the availability of heart-lung bypass as an emergency procedure. It also conserves the patient's own blood volume and permits operations on patients who have religious objections to blood transfusion.

A suction-operated heart-lung apparatus, now under development in the NHI's Laboratory of Technical Development, is about the size of a quart can, is easily disposable, and can be sterilized before use by autoclaving. The support for the membrane lung of the apparatus is a vinyl-coated Fiberglass screen. It is enveloped by a silastic-coated Dacron membrane. The membrane and support are spirally wound around a central cylindrical core in the quart-size unit.

The use of oxygen at subatmospheric pressure is an important feature. In conventional membrane oxygenators, leaks developing in the membrane can allow the escape of gas bubbles into the blood. However, the new apparatus eliminates this hazard because blood is sucked into any holes developing in the membrane (frequently sealing the leak).

A blood pump has been incorporated into the central core of the apparatus. The intermittent application of suction to the core imparts a pumping motion to the soft silastic ventricles of the pump. One-way valves keep the blood flowing forward.

The new apparatus is currently undergoing experimental trials in animals. Although not yet perfected, the apparatus may be the prototype of convenient, cheap, mass produced, and disposable heart-lung machines for open-heart surgery. Further, the very small priming volume would simplify blood procurement problems, reduce the risk of hepatitis or transfusion reactions, and greatly reduce the cost of open-heart operations.

Inadvertent damage to the heart's nerve impulse conduction system is a definite hazard of heart surgery, as these widely branching fibers are invisible to the surgeon. NHI grantees in Milwaukee have developed an electronic probe for locating and mapping these fibers with sound. Their technique promises to reduce the 10- to 15-percent incidence of surgically induced complete heart block which occurs during the repair of certain congenital heart defects. The device detects differences in the electrical properties of the myocardium and the conduction system. It consists of a bipolar detector probe, an impedance bridge, and a speaker which emits an audible tone that changes in pitch when a change in impedance is encountered by the probe. The conduction system was accurately located in 48 of 54 patients, or 89 percent. Heart block occurred only twice, an incidence of 3.7 percent.

Occasionally, during the repair of ventricular septal defects, operative injury may block nerve impulse conduction from the sinoatrial node (the heart's natural pacemaker located in the right atrium) to the ventricles. The ventricles thus lose their normal rhythm and frequently cease beating entirely.

For several years, artificial pacemakers of various types have been available which are used to stimulate and maintain normal heartbeat in patients suffering from this condition. Most of these artificial pacers are portable, transistorized devices, powered by long-life batteries and connected to the heart muscle with thin wire electrodes. One type, which is used by patients who require only short-term stimulation, is strapped to the outside of the body. Other pacers, similar in function but encased in plastic and small enough to be implanted under the skin, have also been developed. These eliminate the need for external leads and are powered by long-life batteries that will perform effectively for periods of up to 5 years. The implantable type of pacemaker is less likely to be damaged, and has a psychological advantage over external pacemakers in that the patient is not as aware of the implanted device and tends not to regard himself as a "heart cripple."

An important innovation now in clinical use is the synchronous cardiac pacemaker developed by a group of NHI grantees in Miami, Fla. This artificial pacemaker makes use of the heart's own natural pacemaker by picking up the natural signal, amplifying it, and then sending it onto the ventricles where it initiates contraction of those chambers. The new device differs from other pacers in that it utilizes normal sinoatrial impulses subject to modification by nervous and hormonal mechanisms. Thus, the impulse rate of the synchronized pacemaker is not fixed, but varies according to the body's circulatory requirements. Other important changes in pacemakers include the use of coiled platinum iridium electrodes designed to prevent electrode breakage, formerly a principal source of pacemaker failure.

Refinements of these techniques for electrical manipulation of the heartbeat led surgeons to deliberately arrest the heart by the continuous application of an electrical current. This made possible delicate intracardiac procedures that could never have been performed in the beating heart. After surgery, the heart was restarted by the flip of a switch.

This technique was devised by Swedish scientists, and first applied clinically in this country in 1960 by Yale scientists. Recently, the use of electrically controlled fibrillatory arrest during open-heart surgery in 89 patients with congenital and acquired heart defects was reported by NHI grantees at the University of Minnesota. The scientists reported that the technique reduced mortality and improved surgical results in their patients. No undesirable side effects related to use of the technique were observed. They reported that the procedure does not interfere with coronary perfusion, and virtually eliminates the hazards of air embolism—an ever present danger during open-heart procedures in which the heartbeat is not interrupted. When electrical fibrillation is used in conjunction with hypothermia and continuous coronary perfusion, the heart can be stopped safely for prolonged periods of time. In five patients, the Minnesota grantees reported the period of arrest exceeded 1½ hours.

Many of the older methods of treating congential heart defects, involving the use of preserved or living tissue grafts, have been superseded by the use of prosthetic parts—artificial blood vessels, valves, patches, and plugs—fashioned from various synthetic materials. Although these artificial parts have certainly broadened the scope and availability of cardiovascular surgery, patients who received the older type grafts are not necessarily at a disadvantage. This is exemplified by the results of a long-term followup study of 12 patients who, 6 to 9 years previously, had undergone surgical removal of congenitally constricted (coarcted) segment of the aorta and insertion of a freeze-dried aortic homograft to restore aoratic continuity. The grant-aided study, involving X-ray visualization of each graft, pressure measurements above and below the point of its insertion, and assessments of heart and kidney functions, disclosed no evidence of graft or abnormal function in any patient.

The particular heart malformation known as atrial septal defect is characterized by the presence of a hole in the muscular partition or septum that normally divides the right and left atria. These are the heart's "collecting" chambers from which venous and arterialized blood, respectively, flows into the two main pumping chambers, the right and left ventricle. (One or more similar defects can occur in the ventricular septum.) Septal defects frequently result in bloodflow through the defect (cardiac shunts) that can hinder the normal oxygenation and transport of blood, and thus impose a progressively increasing burden on the heart and pulmonary circulation.

Fortunately, uncomplicated atrial septal defects are usually corrected with ease and at minimal risk, either by direct suture or by stitching a fabric patch graft over the whole. Experience has shown, however, that operative risk is increased by the occurrence of secondary pulmonary hypertension and, furthermore, that this risk may be prohibitive if the pulmonary pressures become so high as to balance or even reverse a left-to-right shunt.

From animal studies performed several years ago, NHI grantees reasoned that, under conditions of high pulmonary pressures, the atrial shunt acted as a "safety valve" which protected against congestive right-heart failure by allowing some of the excess, dammed-up blood to flow into the left heart where it was more comfortably accommodated. At this time they devised an experimental method for the delayed closure of atrial defects, that would avoid initially high upswings in right heart pressures at the time of surgery, which is when the already weakened heart musculature could least afford them.

According to their method, which they tested in animals, septal defects were repaired with patch grafts containing small perforations about 8.1 millimeters in diameter. These perforations became closed within 7 to 30 days through the gradual deposition of fibrin strands and subsequent ingrowth of fibrous (scar) tissue.

Recently, these findings were confirmed, and the method and concepts subjected to successful clinical trials in four patients, by scientists in the National Heart Institute's Clinic of Surgery. Survival and striking clinical improvement of these four patients, and comparison of the detailed hemodynamic data obtained before and after surgery, point to the sound physiological basis of this technique.

Even more recently, the NHI scientists extended these concepts to embrace, on an experimental basis, high pressure right-to-left shunts through the interventricular septum. They found that, as in atrial shunts, the gradual closure of ventricular septal defects enabled similar adaptations in the heart and lungs that compensated for conditions of markedly increased right-heart pressures. These studies, involving dogs and calves, also showed that the amount of blood flow across the prosthesis and the duration of patency following its implantation, could be predetermined by varying the size and number of perforations in the patch graft.

A mounting realization of the profound physiological effects of septal defects on secondary pulmonary hypertension (which, in many cases, is reversible), led to the postulate that the deliberate surgical creation of a right-to-left shunt may prevent right-heart failure and increase exercise tolerance in patients suffering from primary pulmonary hypertension (which is not reversible and usually leads to death from congestive right-heart failure in 2 to 10 years). This postulate was tested in preliminary animal studies.

First, the blood-damming effects of pulmonary hypertension were simulated in 10 dogs by progressively constricting the main pulmonary artery with an externally adjustable tourniquet. At a second operation, the surgeons established a shunt between the two sides of the heart with a cannula, and then determined the circulatory consequences of this communication while it was open and while it was clamped shut. They report, "In every animal, opening the communication resulted in a right-to-left shunt, a decrease in right ventricular pressure (average 39 percent), a decrease (average 18 percent) in right atrial pressure, a moderate decrease (11 percent) in systemic arterial saturation, and slight rises (average 9 percent) in systemic arterial pressure and cardiac output."

Controlled, corollary experiments, using six additional dogs, demonstrated conclusively that right-to-left shunts actually do protect against heart failure during exercise. As in the previous experiments, the pulmonary artery was constricted to produce right ventricular hypertension in each animal. The surgeons also created a large atrial septal defect in each of three dogs comprising the experimental group; the three remaining animals were used as controls in studying the effects of graded exercise.

The scientists found that moderate exercise significantly increased right-heart pressures and caused slight increases in heart output of control animals, whereas severe exercise invariably resulted in death from right-heart failure. In contrast to these control findings, the three experimental dogs exhibited only slight pressure increases but considerable increases in heart output in response to moderate and severe exercise, and all animals survived with no evidence of heart failure. Thus, the findings suggest that this operation be applied in the treatment of patients with primary pulmonary hypertension.

THERAPEUTIC APPROACHES TO BLOOD COAGULATION PROBLEMS

INTRODUCTION

As the blood flows through the body, the contesting forces within it are held in dynamic equilibrium. After injury, this equilibrium is upset, a complex series of biochemical reactions ensues, and a blood clot is formed to plug the wound and to stop the loss of blood. In every individual, this process occurs countless times during the day. It might be set in motion by major injuries or by surgery, or by such common traumatic experiences as sneezing, shaving, or brushing the teeth.

Clotting or coagulation changes blood from a liquid to a gel: the blood is returned to the liquid state by fibrinolysis. If the equilibrium between these two processes is shifted too far in either direction, the life of the organism is threatened. On the one hand, it might lead to the wholesale formation of clots that plug vital blood vessels and destroy tissues and organs by starvation; on the other, to the failure of wounds to heal or to massive hemorrhage.

Disturbances in this equilibrium appear to be implicated in the development of atherosclerosis and coronary heart disease and in certain of their often deadly consequences, such as coronary occlusion and myocardial infarction.

During the past three decades, much has been learned about the complex mechanisms which control the formation of blood clots. Much less is known about the mechanisms controlling their dissolution.

During coagulation, prothrombin, an active blood protein, is converted to thrombin. This enzyme attacks another protein, fibrinogen, and chops off a number of amino acid links from its protein chain. The result is fibrin, the major constituent of clots. The clot is formed by the aggregation of individual fibrin molecules into a lattice-like structure.

The dissolution of the clot is initiated by a series of steps (nobody is sure of just how many) which lead to the formation of plasminogen activator. This enzyme acts on an inactive protein, plasminogen, to form plasmin. Plasmin is a protein-digesting enzyme. Although it may attack other blood proteins, it has an especially great affinity for fibrin, the staple in its diet. Plasmin breaks up blood clots by digesting their fibrin.

Thus, a substance which is flowing freely in solution in the blood at one moment forms a stable mechanical structure in the next, and may be gone in a third.

The clarification of many of the mechanisms involved in clot formation and dissolution has been one of the great contributions of the modern basic scientist toward opening new pathways for clinical treatment of patients suffering from thromboembolic complications of coronary heart disease.

FIBRINOLYSIS

A tremendous effort has been expended toward harnessing the natural clot-digesting mechanism to man's advantage. Thus far there have been limited, but promising, clinical successes.

Although the natural activator which sets the fibrinolytic system in motion still escapes detection, NHI grantees and other scientists have succeeded in discovering and partially purifying a series of substances which promote fibrinolytic activity in man. However, these substances cannot be purified by conventional protein-separating methods, and the methods which must presently be used leave much to be desired. Because of this, the mode of action of these activators has remained a matter of controversy. Suitable methods for measuring the potency of fibrinolytic preparations are also lacking; and, because of varying reactions in different patients or in the same patient at different times, clinical treatment with these agents must necessarily be highly individualized and carefully controlled.

Another difficulty stems from the nonspecific nature of the protein-digesting enzyme, plasmin. Plasmin may attack not only fibrin, but also fibrinogen and other proteins essential to the clotting process. Thus, excessive plasmin, generated through the action of fibrinolytic agents, might destroy the ability of the vascular system to cope with other vascular injuries and could also lead to hemorrhage, particularly in a patient predisposed to bleeding.

Time is yet another factor in therapy: the fresher the clot, the better the odds on dissolving it. However, in an early case, when chances of successful dissolution are good, the physician may hesitate because of the dangers of side effects and the high cost to his patient. Only later, when the clot is fixed, resistant, and difficult to treat may caution be brushed aside and the risks of side reactions ignored.

What is needed, then, is greater knowledge of methods which will allow man to tamper with the delicate and complex balance of forces of the bloodstream without creating more problems than he cures.

Thus, researchers have concentrated on developing and testing drugs which will activate the fibrinolytic system and which could be administered safely in reliably established dosages. Commercial fibrinolytic agents have been made available for clinical use, but studies by NHI grantees indicate that these products are often neither as pure nor as potent as claimed.

Activation and activators.—A number of substances capable of activating this system have been found in urine (urokinase), blood, the digestive tract (trypsin), and other tissues. It is not yet known to what extent any of the substances participate in fibrinolysis in the body, or even whether certain of them participate.

The fibrinolytic system can also be activated by the bacterial enzymes streptokinase and staphylokinase.

Spontaneous activation can be observed in stored blood or blood preparations, but also takes place as plasminogen is purified and contaminating inhibitory agents are minimized. Trypsin, a digestive enzyme, is a powerful fibrinolytic agent which, early in the unraveling of the fibrinolysis riddle, showed promise because of its effect on inhibiting agents of plasminogen and plasmin. However, its use was discontinued after this early success when it was discovered that trypsin also had a clot accelerating effect at doses needed to digest clots.

An activator is also found in various animal and human tissues, but its isolation and purification has presented great problems—this time because of its insolubility. It is found in highest concentration in pig heart, human uterus, and in conjunction with certain human pathological conditions such as cirrhosis of the liver.

An activator has been found in human blood after electric shock, violent injury, stress, or after heart-lung machine therapy. In fact, the fibrinolytic system was first recognized by John Hunter in 1784, when he observed that blood clotted quickly in men who had met sudden violent death from hanging, but reverted to a liquid state soon afterward. In addition, he demonstrated high fibrinolysis in the blood of deer after they had been run to exhaustion. He then showed that their blood first clotted, then liquified quickly like that of hanged men.

The three activators which exert the most potent effects on the human fibrinolytic system and which have shown the greatest clinical promise thus far are streptokinase, staphylokinase, and urokinase. The first two activators are produced from cultures of streptococcus or staphylococcus and subsequently purified chemically. Urokinase is extracted from human urine and then purified.

Some problems.—Despite diligent efforts over the last decade, the problem of purifying these substances is still a knotty one, and has played a major role in the controversies surrounding their mode of action. For example, it is impossible at times for the investigator to determine whether the active ingredient in his crude mixture is the substance he is attempting to purify or one or more of the "contaminants" he is trying to remove.

The presence of impurities makes for variations in potency between different batches of the drug and for subsequent difficulties in determining proper dosage schedules. This problem is especially perplexing in the case of fibrinolytic agents because it compounds the difficulties already posed by the wide variations in response to these agents among patients.

Impurities also increase the probability of undesirable side effects. Earlier streptokinase preparations were notorious for the high incidence of fever, chills, and other distressing symptoms attending their use. These have been largely eliminated as the result of improved purification methods.

The use of bacterial enzymes as activators poses still another problem. These enzymes are antigenic substances; and almost anyone who has ever had a strep infection will have developed antibodies against streptokinase. The antibody response elicited by streptokinase also makes its use in fibrinolytic therapy strictly a one-shot approach. Its repeated use may cause severe immunologic reactions.

Fewer difficulties on this score can be anticipated with urokinase, a native human protein.

Recent clinical progress.—Despite these adversities, progress in the clinical application of fibrinolytic agents has been substantial during recent years. Investigators are now reporting large series of patients in whom fibrinolytic therapy was employed against thromboembolic disorders with moderate to marked success. To date, however, there have not been sufficiently well controlled experiments to give confidence in the efficacy of fibrinolytic agents studied. Case reports have depended heavily on clinical impressions and studies have been fraught with difficulties from antigenic reactions.

Some investigators have island-hopped uncertainties and controversies concerning the mode of action of these drugs, an admittedly risky enterprise. However, they have avoided many of the potential pitfalls in this approach by devising sensitive techniques for monitoring fibrinolytic activity in individual patients and by using activating substances in connection with inhibitors and fibrinolysis.

One such inhibitor is epsilon-aminocaproic acid, which can slow down the process and prevent runaway lysis of blood protein constituents other than the fibrin of clots. This agent has proved life-saving in the hands of certain investigators when inhibition of the fibrinolytic system was mandatory.

In addition, patients are carefully screened to exclude those with histories of excessive bleeding. Other factors making patients poor prospects for fibrinolytic therapy are abnormal prothrombin time, low platelet counts, allergies, fever, or recent operations, especially on the prostate.

Studies have shown that fibrinolytic therapy may now be considered in cases of venous thrombosis and thrombophlebitis, pulmonary embolism, and peripheral artery thrombosis or embolism. Physicians in India have reported a telescoping of recovery time in a series of heart attack victims treated with fibrinolytic agents. Within a few hours these patients gave evidence of degrees of recovery not attained by the control group until 2 weeks later.

In this country, California grantees have begun a doubleblind study of fibrinolytic therapy in 200 patients with myocardial infarction. This study, begun as a pilot study is designed for expansion into a large scale, cooperative study with multiple participating hospitals and approximately 750 patients. This is, of course, provided that the pilot study demonstrates that this therapy is safe and effective.

Underway at Columbia University is a grantee study on the mechanism of fibrinolytic therapy in obstetrical problems; at Harvard Medical School, a study on the kinetics of fibrinolysis; and at the University of Washington, a study of the effects of lipids on coagulation and fibrinolysis.

These new studies are in addition to continuing support of five groups who have made major contributions to clinical advance in this developing field. These pioneering clinicians have brought fibrinolysis out of the laboratory and into the wards. Collectively they have treated nearly a thousand patients, with encouraging results.

A conference on fibrinolytic agents was held in Chicago in April 1960, to pinpoint the study of current problems in this field and to try to break the logjam of information and conflicting results which have hindered further development. It was discovered that there was no general agreement among investigators concerning mechanisms of action of fibrinolytic agents, much less valid comparisons of their relative effectiveness.

However, there was unanimous agreement that streptokinase is the best agent now available for clinical use and that, on theoretical grounds at least, urokinase will be an even better agent if it can be prepared in a suitably purified form. Last year, following the recommendations of the National Advisory Heart Council, NHI appointed a 10-man Committee on Thrombolytic Agents to advise the Heart Institute on the problems of furthering and strengthening research in fibrinolysis.

Some controversies.—On theoretical grounds, some investigators favor the use of activators such as streptokinase over the use of plasmin or mixtures of activator and plasmin. They contend that the blood contains such large quantities of plasmin inhibitors (antiplasmins) that nearly all infused plasmin will be inactivated before reaching the clot. They feel that massive doses of plasmin would be needed for effective clot lysis, and that such doses would also cause widespread destruction of other blood proteins.

They contend that enough plasminogen is incorporated into the clot during its formation to bring about its own destruction. If this entrapped plasminogen can be converted into plasmin by an activator, the clot will be digested from within. This, they feel, is essentially the mechanism by which streptokinase brings about clot dissolution, although it may be so by stimulating the formation of other activator substances rather than by attacking the clot directly.

Other investigators maintain that plasmin or plasmin-activator mixtures are more effective. They admit that plasmin is probably rapidly tied up by antiplasmins to form plasmin-antiplasmin complexes. However, they contend that while these complexes protect other blood proteins from being attacked by plasmin, they do not protect the clot. The reason is that plasmin has a stronger affinity for fibrin than for the antiplasmin of the complex. Thus, when the complex comes into contact with a clot, plasmin immediately forsakes its inhibitor to attack fibrin.

Some basic studies.—Research is continuing in the attempt to identify natural activators and to develop methods for isolating and purifying such substances. Another line of attack is the search for synthetic compounds which might act directly upon the fibrinolytic system.

A grantee investigator reported that 44 of 126 synthetic compounds tested on preformed human plasma clots showed fibrinolysis-inducing capacities. The study disclosed a definite relationship between the structure of the compounds used and in the activity in plasma. While it is still too early to predict the reactions these compounds will undergo in in vivo experiments, the study points to the strong possibility that a synthetic compound could produce clot lysis.

Another provocative study by NHI grantees showed that fibrinolysis in humans is significantly inhibited by a diet high in saturated fats. Unsaturated fats had very little effect on the fibrinolytic mechanism as compared with saturated fats. This was confirmed by studies with cholesterol where added unsaturated fats actually seemed to inhibit the antifibrinolytic effect of the cholesterol.

Perfection of fibrinolytic therapy would open a new era in the treatment of thromboembolic disorders and perhaps give the practicing physician his greatest weapon toward cutting the mounting death rate from heart disease. However, despite glowing accounts of the accomplishments and potentials of enzyme therapy, the present state of fibrinolytic treatment leaves much to be desired. There are tremendous gaps in fundamental knowledge of the mode of action of fibrinolytic activating agents and difficulties in isolating and purifying these agents and estimating their potency. Moreover, proper evaluation of claims of successful therapy in relatively large groups of patients awaits more carefully controlled clinical studies. Until some of these problems are overcome, this rapidly expanding field is likely to remain a highly controversial one.

ANTICOAGULANTS

While the therapeutic aim of the fibrinolytic agents is to breakup clots already formed, anticoagulants are designed to prevent the formation of the unwanted clot in the first place. Since the processes of coagulation and fibrinolysis, that is, the transformation of blood from a liquid into gel and back again, are seen as a dynamic mechanism, anticoagulants do not block coagulation but rather attempt to modulate or retard it in a manner calculated to induce a carefully controlled bleeding tendency.

Whereas the thrombosis of coronary thrombosis is produced by overcoagulation, suppression of natural coagulation factors, if not carefully controlled, could result in excessive bleeding tendencies and hemorrhagic states resembling hemophilia—thus the range allotted the physician in which to correct a teetered equilibrium among the contesting forces of the blood is a small one.

Agents in use.—The principal anticoagulants now in use are heparin and the coumarin derivatives or related compounds. Both suppress the fibrin clotting system, (one of several clotting systems), but each accomplishes this in a different way.

Heparin, a drug in clinical use for 26 years, is found in liver, lung, and other tissue. It is called a direct anticoagulant since it prevents a final step in the construction of the fibrin superstructure of the blood clot. It is not effective if taken by mouth, so consequently it is given by injection.

The coumarin compounds are called indirect anticoagulants, since they accomplish their mission, not by direct interference with the formation of the clot, but rather by reducing the plasma concentration of certain enzymes needed to catalyze the clotting process. There are literally hundreds of coumarin-type compounds, but only about a dozen are clinically feasible. The most commonly used drugs of this type are phenindione and warfarin.

While anticoagulants were generally accepted therapy in thromboembolic diseases for several years, considerable controversy over their benefits has arisen over the last 18 months. While no one has shown the drugs to be harmful, several teams of investigators have challenged the value of anticoagulants for either short-term or long-term therapy.

At the international anticoagulant symposium held this year opponents of anticoagulant therapy suggested that:

1. Protherapy investigators were not using comparable groups of patients in randomized fashion, and therefore their conclusions were open to question.
2. The "rebound phenomenon"—hypercoagulability that may follow cessation of therapy, may account for the statistical advantage in favor of patients continued on anticoagulants compared with short-term controls.
3. Long-term studies show that anticoagulant therapy offers no advantage after 3 months to a year.

Several recently reported studies support this view.

Danish investigators report that the 4-year mortality in a study of 1,404 patients with acute myocardial infarction totaled 40.9 percent in the anti-coagulant-treated group against 39.9 percent in the untreated group. Excluding patients who died during the first 24 hours, the mortality rate was exactly the same for both groups—28.9 percent. In approximately 800 patients who survived more than 48 hours and formed the basis for the long-term study, the mortality in treated versus nontreated was 22.9 percent against 25.4 percent. NHI grantees at the University of Oregon supported this view with evidence from a double-blind study of 200 patients. The findings of the Oregon investigators suggest that "continuous prophylactic anticoagulant theraphy postmyocardial infarction to date has produced no advantage * * * over placebo or nontreatment.

However, the bulk of evidence presented at the anticoagulant symposium still favored use of anticoagulants to reduce the infarction recurrence rate and the mortality of treated subjects. Cumulative data presented at Miami Beach in late January covering thousands of patients in long-term trials supported this contention.

Studies by California grantees, for example, indicated a lifesaving role for antcoagulants borne out in many other reports. These grantees noted that mortality in the first 48 hours among patients who did not get heparin was 50 percent higher than those who did. A 5- to 15-year grant-aided study of 404 patients at George Washington University Hospital also supports the case for anticoagulants. In the George Washington group, there were 103 survivors (50.4 percent) in treated group and 35 (18 percent) in the control group. Under age 60, a total of 74 patients (36.2 percent) and 21 (10.5) survived in the anticoagulant and control groups, respectively.

Heparin versus oral anticoagulants.—A series of NHI grantee studies suggest that heparin is of greater value as an anticoagulant than the coumarin-type compounds. University of Washington scientists reported that a 3½-year study of two matched groups or patients with "one or more poor risk myocardial infarctions" indicated that the heparin-treated group had a much lower mortality rate and a greater improvement rate. There were 4 deaths (7 percent) and 8 recurrent infarctions (14 percent) among 55 patients treated with heparin. These results contrasted with 11 deaths (20 percent) and 19 recurrences (34 percent) in 55 patients given oral anticoagulants. In addition, the Washington grantees reported that definite progressive improvement of the anginal syndrome occurred in 42 patients (76 percent) receiving heparin, contrasting with improvement in 20 patients (36 percent) on oral therapy.

NHI grantees at Cedars of Lebanon Hospital, Los Angeles, recently reported on 67 patients with severe coronary disease who were treated with 200 milligrams of heparin twice a week for an average of 92 months. The scientists observed symptomatic improvement in 60 to 70 percent of the series, beginning 1 to 2 months after the start of therapy. The yearly mortality was a low 2.9 percent and there were no hemorrhagic deaths. The significant advantage of heparin, according to the investigators, is that, whereas long-term oral anticoagulant therapy has been shown to be ineffective if initiated more than 3 years after onset of overt coronary disease, heparin therapy is effective any time.

University of Southern California investigators also reported a series of 116 patients under treatment from 1 to 13 years with heparin. There were seven deaths in the heparin treated group (6.9 percent) compared with an average of 50 percent in the untreated group of the series.

However, a University of Toronto study indicated that intravenous administration of heparin did not lower the deaths in patients with acute infarction either during the first 48 hours when it was being given or during the subsequent period of convalescence in the hospital. From a group of 101 heparin-treated patients and 105 controls the Canadian investigators reported an overall death rate of 28 and 21 percent, respectively. When the rates were adjusted, no statistical difference was noted between the groups.

Thus, while there is little or no evidence that anticoagulants do any harm in coronary heart disease and much evidence that they are beneficial, some teams of investigators have considerably curbed earlier unrestrained optimism concerning the use of anticoagulants both as therapeutic and as prophylactic measures. The examples cited in this report reflect the controversy in this area. However, even the sharpest of the anticoagulant critics seldom hesitate to use them in acute coronary attacks, and no alternate therapeutic measures have been suggested.

As in the case of fibrinolytic therapy, gaps in basic knowledge pose problems which can hardly be expected to be solved overnight. Moreover, accurate evaluation of claimed clinical successes or failures awaits completion of a large number of the more carefully controlled studies—many of which have been underway for less time than would assure clinical confidence.

SUMMARY

Great strides have been made in recent years toward harnessing the dynamic mechanisms of the blood system for therapy in coronary heart disease and thromboembolism. However, tremendous gaps in fundamental knowledge concerning the dissolution process of the blood make progress difficult and evaluation of that progress harder still. To a great extent, this absence of basic knowledge has been the greatest kindler of controversy. On the other hand, the absence of long-term, carefully controlled clinical studies—many of which are now underway—has also inhibited proper evaluation of clinical successes.

FELLOWSHIPS

Mr. Fogarty. Now you show no increase in fellowships. Have you about caught up with the need for professional personnel in this field?

Dr. Knutti. No, sir.

Mr. Fogarty. If you have not, why do you show no increase?

Dr. Knutti. There is no increase between 1964 and 1965.

TRAINING GRANTS

Mr. Fogarty. You have an increase of $198,000, which is a little over 1 percent for training grants. Will this amount cover the increased costs?

Dr. Knutti. In the training grants area, sir, I think this would be sufficient.

Mr. Fogarty. Will it cover the increased costs?

Dr. Knutti. Sir, I think it will.

Mr. Fogarty. I doubt very much that it will.

BASIC RESEARCH ON GENETIC CODE

On page 215, you indicate you are doing basic research on the so-called genetic code. This work is also being done under "General research and services." How is your work different from theirs, or is it?

Dr. Knutti. Well, sir, this is the work that I refer to here as being done by an intramural research group. This is a direct operation. This particular writeup on page 215 has to do with our own intramural research organization.

Mr. Fogarty. Well, I understand some of the work on research in the genetic code is being done under "General research and services."

Dr. Knutti. Perhaps I could comment on it. Dr. Marshall Nirenberg, who is in charge of this genetic code with in the Heart Institute——

Mr. Fogarty. Has he been in this room at any time during these hearings?

Dr. Knutti. No, sir. He works in the direct research programs of the National Heart Institute and, as you may have read or heard, he has won a number of prizes this year in the work he has done in so-called cracking the genetic code.

There is support for work in genetics relative to various categorical interests that is carried on by several of the categorical institutes, as well as in the Institute of General Medical Sciences. Dr. Nirenberg's work is being carried on by our own research group.

Does that answer your question?

Mr. FOGARTY. That is sufficient.

GEOGRAPHIC STUDIES

What are you finding in your geographic studies?

Dr. KNUTTI. It is a little early to give any results, but I might report about the things that have been planned or are now underway. Last year I testified before this committee on the programs of the collaborative area which include the geographic studies.

One interesting program that has been developed during the past year has been in Puerto Rico. I mentioned last year the fact that we were contemplating this study. In the native Puerto Ricans, the incidence of coronary heart disease is significantly less than the incidence in coronary heart disease in the continental American population as a whole. There is some evidence that the coronary rate in the Puerto Ricans who migrate to New York City and stay there for a while increases and our geographic pathology team is interested in finding out the reasons for this, whether it may be dietary, hereditary, environmental, tension, what factors really lie behind this. But we cannot give you the answers on this yet. The study has been implemented and it is going forward and we have an individual assigned in Puetro Rico to ——

Mr. FOGARTY. There is a study going on with people in Ireland and those who come from Ireland to Boston; is there not? Is that something similar?

Dr. KNUTTI. There is one that is being carried on that has to do with the relatives of the British and the Norwegians who have migrated to this country. In other words, we are doing a dual study. I am not aware, sir, of the study to which you refer.

Mr. FOGARTY. This has been going on 2 or 3 years. It is a study of people in Ireland and their relatives who have come over here. The incidence of heart disease is much higher with the relatives after they have been here a few years than those who stayed behind.

Dr. KNUTTI. I think I know to what you refer now. This is the outgrowth of a study that was started by Dr. Paul Dudley White on Italian migrants.

Mr. FOGARTY. Yes. You are not supporting it at all?

Dr. KNUTTI. We are supporting it.

Mr. FOGARTY. That has been completed?

Dr. KNUTTI. No, sir.

FRAMINGHAM PROJECT

Mr. FOGARTY. All right. What about your Framingham project?

Dr. KNUTTI. That study is continuing. Of course, it is from the Framingham project that we have spelled out the criteria for the coronary-prone individual. The most recent occurrence in that study is that we are building into it a study on cerebrovascular disease, which was really not anticipated when the Framingham study was started.

So in addition now to continuing the study of the epidemiology of heart disease, we are starting on trying to delineate some of the factors that have to do with strokes.

Mr. FOGARTY. You still think it is a worthwhile project, this Framingham project?

Dr. KNUTTI. Yes, sir; I do indeed. I think it has been the indicator for the movement in many directions for research in heart disease, in pointing out in populations those areas which are of importance.

Mr. FOGARTY. You might expand on that statement for the record.

(The information requested follows:)

COLLABORATIVE STUDIES: FRAMINGHAM AND GEOGRAPHICAL PATHOLOGY STUDIES

For 13 years, the Framingham study has intensively investigated factors affecting the development of heart disease in a study population of 5,127 men and women aged 30 to 60 years. This study has yielded important data on the magnitude of heart disease risk associated with such factors as age, sex, elevated serum cholesterol levels, high blood pressure, abnormalities in the electrocardiogram, cigarette smoking, overweight, and various combinations thereof. For example:

Men in their fifties have four times the risk of men in their thirties.

Women tend to develop heart disease some 10 to 20 years later in life than do men, and they also tend to develop less lethal forms of the disease, e.g., angina pectoris rather than acute myocardial infarction.

Men with serum cholesterol levels exceeding 240 mg. percent have more than three times the risk of men with serum cholesterol levels less than 200 mg. percent.

Individuals with systolic blood pressures exceeding 160 millimeters of mercury have four times the risk of individuals with systolic blood pressures less than 120.

Individuals with abnormal electrocardiograms have 2½ times the risk of individuals with normal electrocardiograms.

Cigarette smokers have nearly twice the risk of nonsmokers or persons who smoke pipes or cigars. (This risk factor is reduced to nearly the risk level of nonsmokers for persons who discontinue cigarette smoking.)

Individuals more than 30 percent overweight have about twice the risk of nonobese individuals.

Combinations of the above factors can escalate heart disease risk. Thus: a combination of high blood pressure, elevated serum cholesterol, and ECG abnormalities increases risk more than fivefold; the combination of elevated serum cholesterol, high blood pressure, and cigarette smoking increase it more than tenfold.

The evidence accumulated in this and other epidemiological studies, by identifying factors predisposing to the development of coronary heart disease, has made it possible for physicians to identify highly susceptible individuals long before the disease produces clinical signs, and possibly before it can gain any substantial foothold. Many of these predisposing factors can be ameliorated or corrected; thus the physician is able to initiate measures to postpone the onset of coronary heart disease, or perhaps prevent it altogether.

Many studies during recent years have been concerned with serum lipid patterns as indexes of a predisposition to coronary heart disease. Serum cholesterol levels, the time-honored prognosticator, have been challenged by data indicating that determinations of serum triglyceride levels, the cholesterol-phospholipid ratio, serum lipoprotein patterns, and various combinations thereof, might provide more reliable indexes.

Data from the Framingham study indicate that serum cholesterol levels are still the most reliable single lipid parameter for predicting heart disease risk, and that there appears to be no significant advantage in obtaining batteries of lipid measurements or indexes derived therefrom.

GEOGRAPHIC PATHOLOGY STUDIES

A research team with experience in the Framingham study will be assigned to collaborate with medical groups in Hawaii to study an unusual experiment of opportunity. The pattern of mortality from coronary disease and cerebrovascular disease among persons of Japanese ancestry now living in Hawaii differs so markedly from that found in the United States that it deserves intensive study. The Japanese have a very low incidence of coronary heart disease, but a very high incidence of cerebral vascular disease. This poses a most significant puzzle in the epidemiology of cardiovascular disease. The data gained from the proposed studies could provide important clues to factors that operate in the development of coronary and cerebral vascular disease.

An experiment of opportunity, arising as a result of radiation studies among survivors of the Hiroshima raid, may make possible a more accurate assessment of diet and other factors possibly responsible for the striking differences in heart disease mortality between Japanese and Americans. One of the byproducts of the radiation study has been excellent data on the incidence and severity of cardiovascular disease in this population group. This study may make possible valid comparisons of data from Hiroshima males with similar data from males enrolled in the Framingham study. These data should also prove extremely valuable in connection with epidemiological studies among the American Nisei and Japanese residents of Hawaii.

Plans have been completed for a collaborative study to determine what factors account for the unusually low death rates from coronary heart disease among males aged 40 to 62 in Puerto Rico. The death rate from heart disease among Puerto Rican males in this age group is only one-third that of white males of the same age in the continental United States. The death rate from coronary heart disease among Puerto Rican males who moved to New York City is midway between the island rate and that of white New York males. A major study of this experiment of opportunity is underway.

An important means by which the epidemiologist attempts to evaluate the influence of mode of life and environmental factors on the development of heart disease is through studies comparing population groups in countries where heart disease mortality is low with groups of the same racial stock who have migrated to other countries and have adopted, or are gradually adopting, different modes of life.

Such studies have shown that the Nisei, who have largely adopted westernized ways of life, have about the same mortality from heart disease as do other Americans. Hawaiian-Japanese, who still retain many of their oriental customs and dietary habits, have a heart disease mortality rate higher than that of native Japanese, but much lower than that of the Nisei.

Similar studies currently underway are comparing a group of Italians who have migrated to Boston from Naples with a matched population of Neapolitans, and Irish males who migrated to Boston with their brothers who remained in Ireland.

In the Irish study, approximately 500 Irish Americans are being compared with some 400 brothers still living in Ireland. Data being collected includes: family history, medical history, physical examination, skinfold measurements and other indexes of general body build, occupation and physical activity records, 12-lead electrocardiograms, dietary information, smoking and alcohol consumption data, serum cholesterol determinations, and other biochemical measurements. Preliminary results indicate that the Boston Irish eat more fat, tend to be heavier, and usually have higher serum cholesterol levels than do their brothers in the old country.

Today Israel provides an especially fertile field for epidemiological studies. The influx of Jews from all parts of the world has localized within one small country population groups of widely different ethnic and geographic origin. Striking differences in mode of life exist among certain of these groups, and equally striking differences in the prevalence and severity of heart disease. Comparative studies on these groups provide unusual opportunities to assess the importance of genetic and environmental factors affecting susceptibility to heart disease, and to evaluate the impact of changing modes of life on the incidence of the disease in these population groups as they are assimilated into the Israel culture. Israel also has at her command abundant, highly trained research manpower and the modern research facilities needed to exploit these opportunities.

Presently underway in Israel is a study of hypertension and coronary heart disease among 10,000 male civil service employees over 40 years old. The study population represents a cross section of the various ethnic and demographic segments of the population of Israel. Examination centers have been established in strategically located Government hospitals and standardized procedures devised for the assessment of physical, biochemical, nutritional, psychological, and social factors that may influence the prevalence of these diseases. Examinations and gathering of data began in late 1962. Present plans call for continued observation of the population sample for 5 years, with reexaminations scheduled for 1965 and 1967.

Much of the evidence linking dietary factors, especially dietary fat, to the development of heart disease has emerged from the comparison of data obtained in foreign countries with similar data collected among Americans. Relatively few dietary experiments of opportunity exist within the United States because any sectional differences in habitual dietary patterns that might once have existed have largely vanished in the wake of the general availability of common foodstuffs through our excellent food distribution system.

A few examples:

The Japanese derive only about 10 percent of their total calories from fat, and their mortality rate from heart disease is very low (8.1 percent of all deaths versus 34.5 percent in the United States). Autopsy studies comparing Japanese subjects with Americans from Boston revealed that the onset of coronary heart disease in Japanese subjects occurred about 20 years later than in American subjects and progressed thereafter at a much slower rate. The incidence of heart disease in American subjects aged 20 to 30 was about as high as that in Japanese aged 50 to 60. No Bostonians more than 30 years old were found to be free of heart disease; some Japanese remained free of the disease until their seventies. Fibrous and calcified lesions had become dominant among American subjects by the fifth decade; among the Japanese, such lesions did not predominate until the seventh decade.

In Thailand, the diet is low in total fat, but the bulk of these fat calories are saturated fats derived from lard, the principle source of cooking fat. Autopsy studies comparing Thai subjects with subjects from Los Angeles revealed that, whereas the extent and severity of atherosclerosis of the aorta was very similar in both groups, Thai subjects aged 50 to 90 had only half as much atherosclerosis of the coronary arteries. Fibrotic and calcified lesions developed earlier and progressed more rapidly in the Americans, and complications such as coronary occlusion and myocardial infarction were eight times as common. The scientists concluded from this study that a diet low in fat, though that fat be mainly saturated, is compatible with a low incidence of heart disease.

Somewhat similar findings have come from autopsy studies comparing atherosclerosis in subjects from New Orleans with subjects from Puerto Rico and a number of other Central American countries. Despite marked differences in diet, mode of life, and prevalence of heart disease among these populations, the early development of atherosclerosis appeared to be strikingly similar in all groups. Fatty streaks appear in the arteries of all groups during the first three decades of life. Thereafter, the differences begin to emerge. In Americans and other groups with high mortality from heart disease, the development of fibrons and calcified lesions proceeds more rapidly; and clots, intimal hemorrhages, and other complications are far more common.

CONCLUSION

Epidemiology has been called the major discipline of preventive medicine; and, in our present state of knowldege, prevention of first heart attacks holds forth the greatest hope for reducing our present heavy mortality from coronary heart disease.

Irreplaceable natural experiments occur in human populations resulting in wide differences in the incidence and mortality from cardiovascular diseases. More sophisticated techniques are now available to investigators seeking the factors causing the unusual high rates of such disease in some populations while other similar populations remain relatively less affected by these diseases.

The extensive data gained from epidemiological studies has already resulted in the construction of a highly useful portrait of the coronary-prone individual. This portrait is helping physicians to spot coronary candidates early and to initiate measures that may well save or prolong their lives.

Further investigations in unusual populations can provide a testing ground for additional hypotheses of genetic, biochemical, hematological, dietary, cultural or other factors and their relationships to premature development of heart disease. Epidemiological and geographical disease studies have opened a new area for obtaining important knowledge about these diseases in their natural circumstances in human populations. It is anticipated that important additional knowledge will be obtained through this area of research effort.

USE OF HORMONES AND DRUGS IN PREVENTING MYOCARDIAL INFARCTION

Mr. FOGARTY. Does your present program and budget provide an answer regarding the value of hormones and drugs in the prevention of myocardial infarction?

Dr. KNUTTI. It does for this fiscal year, sir.

Mr. FOGARTY. Tell us about it.

Dr. KNUTTI. If I may, I would like to summarize some background about this study. I am prepared to give a special report to the committee if you so desire.

This cooperative study of drugs and coronary heart disease has been of considerable interest to the Heart Institute for several years. In fact, it was started before I became Director of the Heart Institute.

A little over 3 years ago, the National Advisory Heart Council, which was aware of the needs for research in this particular area, suggested the possibility of a study of drugs that lowered lipid concentration of the bloodstream—this includes cholesterol and other fatty substances—as one aproach to the general problem of atherosclerosis.

Mr. FOGARTY. Has any drug been developed that will lower the cholesterol in blood?

Dr. KNUTTI. There was one that actually was probably as responsible for the stimulation in this field as any, but it has been taken off of the market.

Mr. FOGARTY. Because of bad side effects?

Dr. KNUTTI. Yes, sir. There are others that are known to lower lipids, one or another.

Mr. FOGARTY. All right.

STUDY OF LIPID-LOWERING DRUGS

Dr. KNUTTI. The Heart Council about 3 years ago asked Dr. Robert W. Wilkins, professor of medicine at Boston University, to explore the desirability and feasibility, and methodology of a large-scale cooperative study of lipid-lowering drugs in the treatment of atherosclerotic disease. A small research grant was given to Dr. Wilkins to gather together a consultant committee to explore the problem.

A judgment was reached by this committee on March 4, 1961, that such a study was not only desirable, but was feasible. Based on this evaluation, the committee in subsequent sessions explored the design, the organization, and the budgeting of such a research undertaking.

Early in 1962, a policy board was established to formulate recommendations with regard to a projected national cooperative trial of lipid-lowering drugs in atherosclerotic disease. Through a series of subcommittees and based on many meetings over the past 2 years, these individuals have worked long and hard and have come up with detailed plans for a drug evaluation study in lowering cholesterol and the effects of such agents on individuals who have had one or more attacks of coronary heart disease.

The aims of the study are, first, to evaluate several drugs for their ability to reduce the mortality rate of men who survived one or more myocardial infarctions; second, to determine the degree to which these drugs lower lipids; third, to obtain comparable placebo treated subjects; and fourth, to accumulate further knowledge and experience in the methodology of cooperative drug trials in cardiovascular disease.

Now, the subjects that will be considered eligible for this study will be men aged 30 to 64 who are free from certain specified diseases and who are between 3 and 36 months from their most recent myocardial infarction.

After an initial period of observation, these patients will be assigned randomly in a double-blind study to one of six drugs, the six including the placebo.

After allocation of treatment, the patients will be followed at the participating clinics 4 or 5 years or until death, whichever is earlier.

It is estimated that in order to establish without doubt the 25-percent relative reduction in the 5-year mortality rate—this has been done by our biostatisticians—that there will be 8,400 patients required.

The plans call in the initial year for 300 patients to be studied in five centers. The drugs have been chosen—may I go off the record, sir, for a moment?

Mr. Fogarty. Sure.

(Discussion off the record.)

Dr. Knutti. The compounds which are to be used have been selected. And as I noted, the primary end point in the proposed study will be death from any cause, the said cause to be determined as accurately as possible, so that cause-death rates may also be computed.

The serum lipids—that is, cholesterol, triglycerides, phospholipid—will be measured periodically under controlled conditions by a central laboratory to assure technical uniformity between the groups. The potential drug toxicity will be monitored at followup visits by history and physical examination as well as by hemotologic studies. And then additional determinations will be performed routinely on specimens sent to the central laboratory for biochemical indications of toxic effects. What I am saying is that the monitoring for side effects is going to be very careful so that any drugs that show any deleterious effects or any signs of side effects may be eliminated from the study, and the study is constructed so that drugs may be eliminated or, that as new drugs which might have more promise than the ones that are being used can be built into it.

Mr. Fogarty. The Heart Institute knew of some of these side effects 10 or 12 years ago, at least 10 years ago, in the area of female hormones.

Dr. Knutti. In the area of female hormones—as a matter of fact, any drug, if it is given in sufficient quantity, is a toxic agent.

Mr. Fogarty. I remember them talking about it 10 years ago.

Dr. Knutt. Well, sir, that in a nutshell is what this is about.

Mr. Fogarty. You can expand on this for the record if you think you should.

(The information requested follows:)

THE COOPERATIVE STUDY OF DRUGS AND CORONARY HEART DISEASE

BACKGROUND, DEVELOPMENT, AND ORGANIZATION

For several years now, the National Heart Institute has been interested in whether purposeful lowering of blood lipids, especially cholesterol, over prolonged periods of time would reduce recurrences of heart attacks in men who already have had a heart attack or possibly delay or prevent heart attacks in men who have never sustained one. It need not be pointed out that heart attacks are the No. 1 cause of death in the United States today or that high serum cholesterol levels have been associated with an increased risk for the development of coronary heart disease. It has not been proved definitely, however, whether purposeful lowering of blood lipids for a period of many years would decrease this risk. But the hypothesis that it will do so is an intriguing one which has interested many scientists and physicians for some time. If such a hypothesis were proved to be true, the health implications would, indeed, be far reaching.

Three years ago, the National Advisory Heart Council, cognizant of the need for research in this area, suggested the possibility of lipid-lowering drugs as one approach to this problem. As a result of their interest, the council asked Dr. Robert W. Wilkins of Boston, Mass., to explore the desirability, feasibility, and methodology of a large-scale cooperative study of lipid-lowering drugs in the treatment of atherosclerotic disease. A research grant was awarded for planning purposes. A consultant committee was called together and, after a series of deliberations, a unanimous judgment was reached in 1961 that such a study was not only desirable but feasible.

Based on this evaluation, the consultant committee in subsequent sessions explored aspects of the design, organization, and budgeting of such a research undertaking. These deliberations were reported, and recommendations were made, to the National Advisory Heart Council, which acted to continue grant support for the further development of this planning work.

Early in 1962, a policy board was established to formulate recommendations with regard to a projected national cooperative trial of lipid-lowering drugs in atherosclerotic disease. The policy board recommended that a steering committee be established, made up of investigators experienced in the field, to assume responsibility for research design and protocol development; that a coordinating center be established to provide technical and statistical services for the planning and conduct of the study; and that a technical group be set up consisting of all participating investigators, including members of the steering committee and the coordinating center.

Based on these recommendations, there was convened a meeting of potential participants, serving as consultants, to consider and advise on the work of a steering committee for the proposed long-term study. In a series of meetings during the summer and fall of 1962, this group of consultant "participants" worked as a committee of the whole, and in two subcommittees on design and on criteria. It completed a basic protocol which was subsequently reviewed by the policy board and finally approved unanimously at a joint meeting of the consultant "participants" and policy board in 1963.

Grant applications for the proposed study were submitted to the National Institutes of Health in the fall of 1963. These applications and the proposed study underwent careful scientific review and were the subject of a special meeting of the National Advisory Heart Council in January 1964.

PROPOSED PLANS

The aims of the proposed study are threefold: (1) To evaluate several drugs for their ability to reduce the mortality rate of men who have survived one or more myocardial infarctions; (2) to determine whether the degree to which these drugs lower serum lipids is correlated with any effect on mortality and morbidity rates; and (3) to accumulate further knowledge and experience in the methodology of cooperative drug trials in cardiovascular disease.

Subjects considered eligible for this study will be men, age 30 to 64, who are free from certain specified diseases, and who are between 3 and 36 months from their most recent myocardial infarction. After an initial period of observation, patients will be assigned randomly in a double-blind fashion to one of six regimens. After allocation to treatment, patients will be followed at the participating clinics for 5 years or until death, whichever is earlier.

It is estimated that in order to establish unequivocally a 25-percent relative reduction in 5-year mortality rate, 8,400 patients will be required. In the initial year, 300 patients are to be studied in five centers. This will be followed by the recruitment of additional participating clinics, perhaps ultimately as many as 50, in order to obtain the number of patients required for statistically valid results.

The drugs chosen have been shown to possess serum-lipid-lowering properties, and one of them has already given indications of a favorable effect on mortality (conjugated equine estrogens). They include not only chemical compounds, but also hormones. All are free from evidence of serious toxicity. Provision has been made in the protocol for incorporating into the study selected new drugs that show special promise.

The primary end point in the proposed study will be death from any cause, said cause to be determined as accurately as possible so that cause-specific death rates may also be computed. Other end points such as recurrent myocardial infarction and other cardiovascular events will be evaluated during hospitalization or at clinic visits. Suspected clinical end points will be documented by objective methods whenever possible. In other instances, independent consultant physicians will provide the documentation.

Serum lipids (cholesterol, triglycerides, phospholipids) will be measured periodically under controlled conditions by a central laboratory to assure technical uniformity. Potential drug toxicity will be monitored at followup visits by a history and physical examination as well as hematologic studies. Additional determintaions will be performed routinely on specimens sent to the central laboratory to seek biochemical indications of incipient toxic effects. Detailed criteria for interruption or termination of drug treatment are provided for in the plans for the study.

After 5 years of followup, final analysis of clinical and laboratory data will be made by the coordinating center, and the results will be prepared for publication in collaboration with the clinical participants.

CONCLUSION

Thus, a carefully planned and adequately scaled cooperative investigation of drugs and compounds which have potential of promise for the treatment, reduction, or prevention of coronary heart disease has been the center of significant endeavors on the part of the Institute, National Advisory Heart Council, and scientific review groups and consultants. This new research program has been developed also with regard to the attention focused upon this area of needed heart research by the Appropriations Committee, which in the past has expressed strong interest in development of its potential. As has been noted by the National Advisory Heart Council, the value of a well-planned, controlled clinical trial of drugs for coronary heart disease is such that the proposed cooperative study offers promise of a high yield of information for the investment.

Mr. FOGARTY. You have mentioned the Heart Council's program activities. Has the Council made any attempt to price out these programs? They generally come up with their own recommendations for the budget.

Dr. KNUTTI. In their program activities, they obviously are concerned with the costs of various programs which they feel are worthy of development. This is, of course, not only in line with their interest in substantive research, but also in their responsibility in their role as advising the Surgeon General of which projects should or should not be recommended for approval.

Mr. FOGARTY. The Heart Council is generally a pretty conservative group, is it not, when you compare them with other councils and voluntary organizations?

Dr. KNUTTI. Sir, I have been associated with two institutes——

Mr. FOGARTY. I have been told that many times, talking about the Heart Association and other councils.

Dr. KNUTTI. I would generally say that in my experience there is not much variation in the relative conservatism of councils as a whole.

Mr. Fogarty. There is with the voluntary national associations?

Dr. Knutti. Yes, sir.

Mr. Fogarty. The National Heart Association I have been told has always been on the conservative side, compared to American Cancer Society for instance.

Dr. Knutti. I have not had enough experience with them to make any personal comment on it.

Mr. Fogarty. I do not want to put you on the spot. I just was repeating some things I heard.

Mr. Lesinski?

Mr. Lesinski. One question I had was asked by the chairman and you have answered it.

CAUSE OF HEART FAILURE

I am convinced that hypertension is one of the biggest causes of heart failure. I was going to ask you if you had any study for natives of various countries compared with what we have in this country?

Dr. Knutti. We are engaged at this moment, and I mentioned this briefly last year, in investigating the alleged differences between the rates of cerebrovascular disease, strokes, hypertension, and coronary disease, not only among the Puerto Ricians, but among the Japanese. It is fairly well documented that in the Japanese living in Japan, there is a high rate of hypertension and a very high death rate from strokes relative to the rate in this country.

Mr. Lesinski. In the cities or on the farm?

Dr. Knutti. Well, this has not been studied, sir. There is, at the present time, a study going on in Japan which is centered at Osaka where the investigator is studying two villages and the city of Osaka itself. So if this works out properly, we may have some information on this point relative to these two Japanese villages and the city. To the best of my knowledge, such information is not available here, but we will include it in the information requested which we will submit on Framingham and other geographical projects.

Mr. Fogarty. Some people, like Dr. White, have done similar studies I know. Take Italy, for example, the comparison between the city of Naples right after the war when people were not getting enough to eat and 100 or so miles from there in the country section of Italy, where they had cream and butter and all of these things. I remember he testified before the committee and said the incidence was many times higher in this area in the country than it was in the poorer section in Naples.

Dr. Knutti. That is correct.

My response to your question, Mr. Lesinki, was in terms of: Do we really know this? We have certain leads here and there about certain differences, but statistically I feel that we do not know enough about enough individuals yet to be able to button this up.

Mr. Lesinski. You addressed yourself to hypertension and I addressed myself to diet because diet has a big bearing upon heart also because of too fatty of a diet, large amounts of butter and especially pork has a bearing upon the heart also as cholesterol. But I think hypertension is one of the great factors, and I brought the subject up because if you can compare a rather easygoing farmer—which, of course, is not always true—with a rapidly going executive, there is a big difference between the two hearts. One is simply going along and the other is not—he is always running. In the end, the executive is more apt to have the heart attack regardless of diet and the farmer will keep on living. That is what I am trying to point out to you.

Mr. FOGARTY. Doctor, during the war, I remember people saying in China there was a lower incidence of hypertension and heart disease. It was explained at that time that they thought it was because they were not getting enough to eat, they were half starved, and also maybe the rice diet might have some bearing on it.

Has anything ever been developed on that?

Dr. KNUTTI. I remember a few years ago—oh, I should say 10 or 12 years ago—there were some studies being supported as to the effects of the rice diet on hypertension. In the hands of one or two individuals, one in particular, results seemed to be quite promising.

Mr. FOGARTY. I remember 15 years ago, studies were being conducted at Duke University, I think, on rice diet.

Mr. LESINSKI. Mr. Chairman, people eating whole rice did not have heart trouble, but those eating polished rice did.

Mr. FOGARTY. Yes, we discussed it last year.

Mr. LESINSKI. In other words, the lack of nutrition did have some bearing upon having a healthy heart, those eating polished rice did not survive as long.

Dr. KNUTTI. This is perfectly true, Mr. Lesinski. Polished rice knocks off the hull where the vitamins, particularly the B vitamins, are located. There is one type of heart disease, beriberi heart disease, which is caused by deficiency of vitamin B_1. So if you eat a diet which has no vitamin B_1 in it, you are susceptible to beriberi heart disease.

Mr. LESINSKI. More susceptible?

Dr. KNUTTI. Well, you are very susceptible to it.

Mr. FOGARTY. Do you have any research projects in China today?

Dr. KNUTTI. Well, not with what is commonly referred to as Red China, sir.

Mr. FOGARTY. That is what I mean, Red China.

Dr. KNUTTI. The Heart Institute supports no projects in Nationalist China, but research is going on there. This is a fruitful area for the type of epidemiologic study that we have been talking about, because they have fine hospitals; they have two medical schools in Taipei. Their professional staffs are well trained. It is really a great potential field for this type of study.

Mr. FOGARTY. Mr. Denton?

HARDENING OF THE ARTERIES

Mr. DENTON. I asked this question of the people on aging. One thing I hear an awful lot of is people, when they get a little bit older, have hardening of the arteries and that causes them to have strokes or sometimes they become mental cases, cannot remember anything, a form of mental illness.

One reason I was late, I was working on a problem of that kind in the office today with a constituent. I see an awful lot of it. I guess it is a problem just of aging. But some people have it earlier than others.

Has anything been done along that line?

Dr. KNUTTI. I am sorry, sir, I am not quite sure what is the specific problem.

Mr. DENTON. The problem of hardening of the arteries with the aging.

I expect that is just because you get old, but is anything being done about it?

Dr. KNUTTI. As we get older, in our experience, our arteries harden.

Mr. DENTON. Yes.

Dr. KNUTTI. Now, this varies among individuals. If you would take, I suspect, 100 people who died at the age of 80, you would find some who had very, very marked arteriosclerosis, and you would find some who might not have very marked arteriosclerosis. In other words, there are factors that we do not know about and which we are engaged in studying now that cause people to have arteriosclerosis——

Mr. DENTON. That is what I want to know.

Dr. KNUTTI (continuing). Which are not necessarily connected with the aging process.

Mr. DENTON. Well, you are studying what is causing hardening of the arteries and, in that connection, have you considered the question, what age has to do with it?

Dr. KNUTTI. Yes, sir; we are very much interested in what age has to do with it, because it is so very directly associated with age. I think maybe, sir, this is one reason, if I may volunteer a theory, why we in the medical profession have been so long in coming around to the broad attack on the field of atherosclerosis, because we have felt in the past this is the result of aging and there is nothing we can do about it.

Mr. DENTON. That is what I am trying to get at. One reason, I think age is not necessarily the major factor, because some people get it quite a bit younger than others and some people get quite old without having hardening of the arteries.

Dr. KNUTTI. Right, sir.

Mr. LESINSKI. But are not diet and heredity primary factors?

Dr. KNUTTI. Sir, this is what we are trying to find out. This is one reason why we are supporting a feasibility study on diet and heart disease, which has been going on now for almost 2 years. If I may address myself to this particular study for a moment, Mr. Chairman, I think there has been some confusion, particularly in the press, about the motives behind this study. We read stories indicating that this is going to lead into a large-scale definitive study, including 100,000 American males in this age group.

Actually the purpose of the study now being conducted is to determine whether or not it is feasible and possible to change the diets of the healthy, working American male and whether it is possible to have him stay on the different diets which are being fed to him in this feasibility study for a sufficient period of time that if this were done on a big scale, it would have statistical significance.

I would like to emphasize the fact that the study that is now going on, which is big enough and expensive enough as it is, is but a feasibility study to determine whether or not a big study can or should be done.

EFFECT OF HEART TROUBLE ON LIVING PATTERNS

Mr. DENTON. I saw a television program about heart trouble this last week and former President Eisenhower was on it, General Eisenhower. It seemed to me the main thing they emphasized, if you had heart trouble, just go about leading a normal life after it was over.

Am I right about that or not? Did I get the wrong idea?

Dr. KNUTTI. Yes, sir, I saw the same program. As a matter of fact, the physician who was on that show was Dr. Andrus, who is chairman of the 1965 conference.

I think that one of the things that was pointed out in this production was that it is possible for an individual who has had a heart attack to come back and lead a relatively normal and productive and happy life.

Mr. DENTON. I know General Eisenhower emphasized that fact.

That is all.

Mr. FOGARTY. Did I read something in the paper recently, Doctor, that people in their early forties who may have had a coronary and who smoked excessively, that they had a better chance of survival if they gave up smoking?

Dr. KNUTTI. There is some evidence to this effect.

Mr. FOGARTY. There was an article in the paper recently about that.

Dr. KNUTTI. This is one of the findings that has come out of the seven studies which were referred to in the Surgeon General's report on tobacco and heart disease. As a matter of fact, I think the first, and perhaps the most important one, came out of the Framingham study itself, that individuals who stop smoking have a better chance of not having coronaries than those who continue to smoke.

Mr. FOGARTY. This article I referred to, was about people who had been and then stopped.

Dr. KNUTTI. I think that most physicians would advise their patients who had coronaries to stop smoking because of implications that are already known about the effect of tobacco on coronary heart disease.

Mr. FOGARTY. Is there anything else you want to say, Doctor?

Excuse me, Mr. Lesinski, are you through?

Mr. LESINSKI. No; I just had one more thought. I have no more questions, but I want to verify that it was a matter of diet, environment, and exercise, the basis of the condition of your heart. Because a person, if he does not exercise, his body becomes toxic and poisonous and therefore you have a greater effect on your heart.

EFFECT OF ALCOHOL ON ARTERIES

There is also a theory that those who drink, like whisky, have less chances of having a heart attack because their arteries are softer. But I think that has been quite amiss because they may be softer for awhile, but they become harder later on.

Am I right or wrong.

Dr. KNUTTI. Well, sir, there are many theories about the effects of smoking and drinking. As a matter of fact, I used to hear that perhaps drinking was not too bad as far as hypertension was concerned, because it relaxed the arteries. I do not think anybody really knows the answers to these questions.

Mr. LESINSKI. The point I was alluding to is the fact it does relax you and thus relaxes the arteries, is that correct? But a continual use over many years will harden them because an opposite effect will take place.

Take a piece of rubber, it is soft the more you bend it but eventually it will break or become hard.

Your arteries will relax and become less tense and softer with alcohol, but in time it will have the opposite effect upon them.

Dr. KNUTTI. I do not think, sir, that we have any evidence that alcohol causes hardening of the arteries in the living individual.

Mr. LESINSKI. Well, if the diet is not supplemented, if that is not properly supplemented? Do people who tend to drink too much not eat very much?

Dr. KNUTTI. Well, I think I see what you mean, Mr. Lesinski. You mean that a person who drinks might eat things and his diet might fail to contain things which, if he did eat, would have an effect on the ultimate production of atherosclerosis?

Mr. LESINSKI. That is correct.

Dr. KNUTTI. I think there is a point there, but I would hesitate to be able to identify those substances which might be referred to.

Mr. LESINSKI. On the opposite side, you take people who drink all their lives live to be 105 or 95, and so on.

Mr. FOGARTY. Is there anything else you want to say, Doctor?

Dr. KNUTTI. I think not, sir.

Mr. FOGARTY. We will put your complete statement in, then you will have all these other statements we have referred to in the record.

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. Thank you very much.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. FRANCIS A. ARNOLD, JR., DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
MRS. FRANCES H. PETTINATO, BUDGET OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH
B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH
LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH
DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL
LOYAL FISHER, DEPUTY DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

		1963 actual	1964 estimate	1965 estimate
11	Personnel compensation:			
	Permanent positions	1,678	1,960	2,122
	Positions other than permanent	25	26	26
	Other personnel compensation	19	31	26
	Total personnel compensation	1,722	2,017	2,173
12	Personnel benefits	209	226	237
21	Travel and transportation of persons	92	139	144
22	Transportation of things	12	9	11
23	Rent, communications, and utilities	57	55	58
24	Printing and reproduction	1	3	3
25	Other services	166	669	671
	Payment to National Institutes of Health management fund	1,004	1,099	1,159
26	Supplies and materials	256	273	291
31	Equipment	135	92	73
41	Grants, subsidies, and contributions	13,803	14,565	15,322
	Subtotal	17,457	19,147	20,142
	Deduct quarters and subsistence charges	6	7	7
	Total obligations	17,451	19,140	20,135

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	258	271	277
Full-time equivalent of other positions	5	5	5
Average number of all employees	246	260	264
Employees in permanent positions, end of year	242	265	271
Employees in other positions, end of year	7	11	11
Average GS grade	7.2	7.4	7.4
Average GS salary	$6,556	$7,037	$7,046

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	8,904	8,898	9,415
(*b*) Fellowships	1,202	1,191	1,199
(*c*) Training	3,698	4,476	4,708
Total, grants	13,804	14,565	15,322
2. Direct operations:			
(*a*) Research	3,019	3,286	3,482
(*b*) Collaborative studies		565	565
(*c*) Review and approval of grants	437	533	554
(*d*) Program direction	181	191	212
Total, direct operations	3,637	4,575	4,813
Total program costs, funded [1]	17,441	19,140	20,135
Change in selected resources [2]	10		
Total obligations	17,451	19,140	20,135
Financing:			
Comparative transfers to other accounts	2,688		
Unobligated balance lapsing	1,060	26	
New obligational authority	21,199	19,166	20,135
New obligational authority:			
Appropriation	21,199	19,689	20,135
Transferred to "National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−523	
Appropriation (adjusted)	21,199	19,166	20,135

[1] Includes capital outlay as follows: 1963, $162,000; 1964, $92,000; 1965, $73,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $102,000 (1963 adjustment. −$1,000); 1963, $110,000; 1964, $110,000; 1965, $110,000.

Mr. FOGARTY. We now have Dr. Arnold with us, Director of the Institute of Dental Research.

GENERAL STATEMENT

Dr. ARNOLD. Mr. Chairman, as you are aware, the full statement of our Institute has been submitted to the committee.

Mr. FOGARTY. Yes, sir; go ahead and summarize it.

(The prepared statement follows:)

Mr. Chairman and members of the committee, this year, for the 15th time, the National Institute of Dental Research is presenting its statement to your committee. It is the 10th time I have had the honor to appear before you to make this presentation. In view of these anniversaries, I think it is worthwhile to look not only at the research accomplishments in our field for the past year, but to place these accomplishments in some perspective in the light of the total program over the years.

Dental research had been conducted before June 1948 when the Dental Institute was established by act of Congress, but its formal identification with the Federal Government began with the handful of research scientists who used the first half-million-dollar appropriation and began their investigations into the causes, prevention, and treatment of oral diseases. They realized that they were dealing with disease entities which, although rarely fatal, were destructive, painful, incapacitating, and expensive to the American people. They also recognized that while oral diseases might be less dire, deforming, and dreadful than poliomyelitis, for example, they had an all-important distinction: they were just about universal. This "distinction" is still present.

Two factors are immediately apparent: (1) the almost universal prevalence of oral diseases; and (2) the relative lack of attention which these diseases have had.

Every survey made by health authorities and organizations has shown that dental decay is the most prevalent of all diseases. Every survey has also shown that almost all our older population is suffering from some form of periodontal disease. In fact, more than 75 percent of people over 60 require dentures as a consequence of this disease.

There are probably nearly a billion unfilled cavities in the United States. There are over 100 million people who have lost teeth because of diseases of the gums and supporting structures. There are more than 6,000 children born each year with cleft lip and palate. Half the children under 15 in the United States have never been to a dentist at all.

In the fact of so monumental a problem, so universal in its involvement, research offers our chief hope.

BACKGROUND

Although some beginning had been made in dental research earlier, the first appropriation to the Dental Institute brought organizational identity and a new direction to the program. A small staff started on early investigations of dental caries, mottling of teeth, periodontal disease, nutrition. These studies were a continuation of the research which has led to one of our greatest boons—the fluoridation of communal water supplies for the reduction of tooth decay. The Institute appropriations produced more fundamental research.

Two years after the Institute was established, another small budget was added for research grant awards. This program expanded slowly until 1957, by which time the allocation for grants to universities and research institutions had increased to almost $4 million. With this increase, dental research awaiting attention outgrew the numbers of dental research workers available. Accordingly, in 1958 an expanded program of grants for fellowships and research training was implemented to increase our resource of scientific manpower.

Two trends were established: an increasing responsibility for support of research and an increasing emphasis on training.

Concomitant with this growth in sheer size, we have had similar development in the complexity and nature of the programs encompassed both inside and outside the Institute. We have seen a more fundamental approach to research and an increasing use of multidisciplinary attacks on research problems. This has been manifested by the many collaborative programs conducted in our laboratories and the many disciplines and skills mobilized in our grants areas. The total approach has been particularly marked in broad-gage approaches to the study of dental caries, oral ulcerations and cleft palate.

The 15 years of the Dental Institute have thus seen important changes—growth in manpower, growth in research and development of newer and more sophisticated instrumentation. Most fundamental of all, we have seen a change in attitude—a receptivity to research and its uses.

The virtual conquest of the acute illnesses which plagued our parents and grandparents has made it possible for our generation to turn to the chronic ailments which do not kill rapidly, but which destroy slowly. The importance of improving health has been added to the importance of treating disease. We are literally on the threshold of a new era.

RESEARCH PROGRESS

Fluoride studies

It is all but impossible to draw a line to delineate research accomplishments for a single year. Research is a step-by-step process in which the activities of each year are the transition from the developments of prior years and the bases for the following year. There is rarely a point at which we can say "This piece of research is finished." Usually the completion of one set of experiments or the development of one finding is the stepping stone to the next problem.

A case in point is the research on the use of fluorides in the control of dental caries—an activity in which this Institute has been involved since its inception. The early studies of fluoride covered its natural occurrence in the drinking water of certain areas and the biological effects of high concentration. Following the determination of optimum levels for caries control, studies showed ways of adding fluoride to water supplies where natural fluoridation was absent or inadequate in concentration. The establishment of optimum levels of fluoridation to effect significant control of dental decay, a better understanding of the way in which fluoride acts, and other contributions soon followed.

Today, more than 50 million Americans are drinking fluoridated water, and the scientific knowledge of the use of fluoride for the control of dental decay is well established.

However, research in fluoride and fluoride metabolism still continues. Recent studies have shown that the decay-inhibiting effects of fluoridation carry over into adult life. Studies with the electron microscope and X-ray diffraction provide important information on the way in which fluoride works, affecting the crystal structure of bones and teeth to render the crystals themselves larger, more perfectly structured, and less soluble in acids.

Investigators are now seeking ways of administering fluorides to populations where the water supply cannot be fluoridated: tablets, topical solutions, and the possible use of a salt vehicle are under investigation.

Two further interesting research developments have begun: one is a study in which a grantee in Sweden is using radioisotopes to determine whether fluoride administered in pregnancy can provide protection to offspring. Another is a collaborative study involving several institutions, to determine the effect of fluoride on bone metabolism, contributing to our knowledge of alveolar bone resorption and perhaps to the treatment of osteoporosis.

Periodontal disease

Periodontal disease—known to many people as pyorrhea—is the major cause of loss of teeth in adulthood. As I have already indicated, the percentages of people who have lost all their teeth to this disease are startling. In 80 percent of our older population the structures which support the teeth have become so diseased that healthy teeth are lost. The seriousness of this problem is such that we have made this topic the subject of a special report, a copy of which is submitted for the record.

I shall mention here only a few significant recent findings. Dental Institute research has established that in hamsters a disease very like human periodontal disease is a transmissible process, caused by a particular micro-organism, described as a filamentous nocardia-like microbe.

Further investigations have been carried on to establish the way bacteria (which are always present in the mouth) mineralize to produce the hard calculus which is one of the important factors contributing to periodontal disease. It appears from the research done that many varieties of oral bacteria can mineralize equally well, particularly after they die. However, only the gram-negative bacteria and the spirochetes contain the lipopolysaccharide endotoxins important in the inflammatory phase of human periodontal disease.

Enzyme chemists at the Dental Institute have directed their research particularly to the structure of the molecules which participate in enzyme reactions to determine enzymatic factors which break down protein substances.

It has been found that the kind of protein (not the amount) in the diet possibly influences the extent of bone loss in periodontal disease. In animals in which periodontal disease has been induced, a high casein diet produced little bone loss, but protein in the form of soybeans produced considerable bone loss.

Institute epidemiologists have shown that periodontal disease is a worldwide problem, causing more tooth loss than any other condition; it is much greater than the problem of dental decay. Early in onset, it is destructive to populations regardless of age and with little respect to geography. While no nutritional correlations have been established to date, a significant relationship has been confirmed between periodontal disease, increasing age and poor oral hygiene. Current knowledge indicates that careful cleansing of the teeth at and below the gum line is the most important preventive we can use.

Dental caries

Tooth decay, which has been a problem among younger populations for years, has yielded measurably to several research accomplishments. For example, a grantee at the Forsyth Dental Center in Boston has done research which points out that teeth treated with a phosphate-fluoride solution are even more resistant to caries than those treated with fluoride alone.

In another approach, developed over the past few years, it has been shown that in hamsters and rats dental caries is an infectious and transmissible disease, requiring specific bacteria, specific dietary factors and host susceptibility. This knowledge is now being carried to the study of the human disease. Investigators are attempting to determine how the caries-producing streptococcus differs from similar bacteria which do not have the same effect.

Research workers are also studying the caries pattern in children who have a rampant form of this disease to determine whether a multiple approach, utilizing advanced instrumentation, fluorescent antibody technique to trace specific microorganisms, and antibacterial medications applied in new and different methods will control the disease in its most virulent form.

Clinical investigations

Important work has been done by Dental Institute investigators in elucidating the causes of such bothersome and difficult conditions as herpes simplex (fever blisters) and aphthous stomatitis (canker sores). These conditions of unknown origin have been notoriously resistant to treatment.

We can now report the isolation of a particular transitional form of bacteria, resembling the pleuro-pneumonia like organisms, from the oral tissues and the bloodstream of persons suffering from recurrent attacks of canker sores. This finding may provide us with a clue to the cause and ultimately to the effective treatment of the disease.

In another laboratory of the Dental Institute, comparisons have been made of virus strains related to recurrent attacks of so-called cold sores or fever blisters. Oddly enough, in four different individuals, each of whom had a succession of painful mouth lesions over a 3-year period, 13 different virus strains could be identified. The mechanism of recurrent infection is, therefore, more than simply the mutation of a single virus. Since antigenically different strains are involved, immunity is not developed. Further investigation is now going on to determine how the herpes simplex virus damages the cells in which it is found.

In an extensive 5-year program, Dental Institute scientists have evaluated general anesthetic agents used in oral surgery and reported a number of significant findings. They have observed a consistent pattern of increased blood pressure, preoperative and postoperative tachycardia, and depression of arterial oxygen saturation. These findings are of importance to both physician and dentist since they provide baseline physiological data essential for the adequate assessment of newly developed anesthetic agents to be used for ambulatory patients.

The Institute also carried out studies of the dental pulp response to newer instrumentation procedures and restorative filling materials. Important data have been assembled on optimal cutting speeds, proper use of coolants, modifications in operative techniques and other practical guidelines to better dental treatment.

Cleft palate

In fiscal year 1963 there has been great expansion of the Dental Institute's program in cleft palate research. Two new multidisciplinary research centers have been established with grant funds, bringing the total of such centers to six. Fundamental research in the genetic background of the cleft palate patient in these centers is accompanied by research in surgery, orthodontics, prosthodontics, speech, and hearing, and psychiatry. The social and psychological rehabilitation of the cleft palate patient is emphasized. Sophisticated equipment and sensitive techniques are applied to derive new bodies of knowledge.

In addition, two conferences were held under grants from this Institute to familiarize speech therapists, speech pathologists and communications workers in the problems of the cleft palate patient.

Research in the cleft palate field has extended and is the subject of a special report.

In our direct operating programs at the Dental Institute, research is proceeding to define the pathogenesis of oral and facial anomalies in animal model systems. For example, certain drugs are being identified that will produce deformities in the rat, including a high proportion of clefts. Other possible teratogenic (deformity-producing) techniques are being studied such as alteration of amniotic fluid pressure, to see if the causes of cleft palate can be better identified.

Growth and development

Particular attention has been given in our clinical and laboratory programs to the palate and neighboring pharyngeal structures in order to elucidate the processes of speech, swallowing, and respiration. These studies have led to such findings as the identification of a local reflex system by which respiration is modified; the anatomical charting of oral sensation as a guide to oral function; and the description of functional compensations for oral and pharyngeal anomalies of development.

In the field of genetics, our scientists have made progress in studying the immune factors which lead one animal to reject transplants from another. By special immunizing procedures, some kinds of monkeys have been made to produce a variety of serum antigens of man and other primates. Through these studies, we are attempting to find a site for transplantation and a time of transplantation for human cells that will then grow in an animal.

A detailed cytogenetic study of chromosome changes involved in cells transformed from benign to malignant by simian vacuolating virus (SV–40) shows that the genetic material (DNA) of the virus is incorporated into the chromosomal DNA of the cells.

It has been found that genetic factors in various oral conditions ranging from tooth decay to cleft palate contribute a small but significant variable to resistance and susceptibility to caries. The ability to taste a chemical called phenylthiocarbamide, which is associated with dental caries, has been established as an inherited trait in two populations, and is now being further elucidated in the laboratory.

Dental materials

The whole field of materials science has undergone dramatic change in recent years. The utilization of the high speed drill and new cutting devices and procedures has revolutionized dental practice. A conference on adhesive restorative materials has contributed significantly to the initiation of research projects by both grants and contracts.

A particularly important program is attempting to develop filling materials that will bond with tooth structure.

The vital significance of this is summarized in a special report of our current activities in this field, which is being submitted for the record.

RESEARCH GRANTS ACTIVITIES

Research accomplishments by grantees—at least a few of the outstanding ones—have been outlined. In summary, as of November 1, 1963, there were 399 research projects supported by the Dental Institute in 129 universities and research institutions, including all the dental schools of this country.

Several significant comments can be made about this program. It represents a slight growth over the last year in number of research grants and number of institutions represented. Most notably, however, it represents an increase in size and complexity of research activity. We find that the average research grant awarded for the first time by the Dental Institute this year is more than twice what a new grant was only 3 years ago, indicating that the research is costlier, more sophisticated, involving a larger number of scientists and a greater number of disciplines.

We have seen this year the inauguration of a series of program-project grants in various fields at several universities, some with dental schools and some without. These program projects cover multidisciplinary research by teams of investigators in broad and basic fields, with several activities combined toward a single overall program. Cleft palate is being studied in this way at several centers. A large program in an engineering school is developing techniques of neutron diffraction, important in the study of calcified tissues. A similar program in a research hospital affiliated with a university is studying the crystal structure of mineral tissues, particularly in aging. Large awards have been made for the study of the temporomandibular joint, biophysical studies of tooth defects and cell differentiation. These programs include studies of protein synthesis, genetic coding, energy flow, and information exchanges between cells.

MANPOWER AND TRAINING

Dental research, like many other of the biomedical research disciplines, is suffering from a shortage of available research manpower. Efforts have been made by the Dental Institute to improve this situation in several ways: by providing training grants in dental research to universities, by providing fellowships to qualified individuals, and by research career awards and research career development awards to provide stable career opportunities in dental research.

The Dental Institute is pursuing the following course: (1) We have increased the numbers of training grants in the disciplines basic to dental research, encouraging trainees to secure Ph. D. degrees in these disciplines. (2) We have inaugurated a new clinical research training program to develop clinical research scientists through a path of study leading to a Ph. D. degree plus eligibility for a board certification in a dental specialty. The first grant under this program has recently been awarded to the University of Minnesota. (3) We are continuing the career award program for appropriately qualified individuals and institutions. (4) We have developed training programs in university environments with specialized competences of importance to dental research but where the university has no dental school. Acute shortages of investigators exist in certain disciplines of great relevance to dental problems. There is particular need for investigators with training in metallurgy, ceramics, polymer chemistry, colloid chemistry, etc. The number of these basic science programs in nondental school environments has increased fivefold during calendar 1963.

Dental Institute support of 78 separate training programs was operative in fiscal year 1963 in 55 institutions, providing training opportunities for some 375 potential scientists.

During fiscal year 1963, 101 regular fellowships were awarded, an increase of 14, and 37 research career development awards were made, an increase of 21 over the year before. A first research career award has recently been made by the Dental Institute.

DENTAL RESEARCH CENTERS

It is recognized that in order to have dental research step into another order of magnitude, institutes or centers devoted to dental research will be needed in many parts of the country. Broad-based clinical and basic research should be part of this program, utilizing the skills and knowledge of scientists coming through the training programs. As research moves into more extensive and more fundamental projects, the need for such broad-based research centers is increasingly recognized.

Eight letters of intent to apply for support for the construction of such facilities have been received. Two awards have recently been made by the Division of Research Facilities and Resources to permit construction of such research centers.

CONCLUSION

In the course of development of every program there are problems. One feature of this kind of problem is that the "bottleneck" moves along to one phase after another. The administrators of a program try to use the forces which are available to them to ease these bottlenecks and move nearer to solutions. In dental research, several such "bottlenecks" have been solved, thanks to the work of this committee, the Congress, and the exceptional devotion of the scientific community in the Institute.

The first bottleneck was getting the Institute started, recognition of dental research as an area meriting institute status. This was solved by act of Congress.

Second came the recruitment of a research team. From 1948 to 1955 this was a major effort (and it continues today).

The ensuing bottleneck in research facilities was solved in two ways: First, by expansion of research through a program of extramural grants; second, by erection of a research building for the Dental Institute in Bethesda.

Current bottlenecks are in manpower. With the expansion of research, it became clear that available manpower would be inadequate. Therefore, the emphasis of the past 2 years, and probably the emphasis for the next few will have to be on manpower: Recruitment of research-minded students into dental schools, development of a cadre of Ph. D. scientists in basic disciplines working on oral health problems, and developing resources both in dental schools and in general university environments to stimulate study in the fundamental areas of dental research.

We can already visualize the problems to come. With the great need for research and the expansion of research manpower, where are these people to work? Answers lie in the improvement of research facilities and the creation of dental research centers or institutes.

The problem that will next arise is the need for communicating research findings to scientists, practitioners, and the public, so that scientific advances will be speedily put to work for the welfare of our people. Some preparatory work is already going on to cope with this problem.

As each phase of this developmental process has come along, we have faced it, created task forces to meet it, and developed plans of operation. The results have been measurable and important: Significant increases in research grants, in training and fellowships, and in manpower in training, the inauguration of research career award programs, dental institutes, program projects, clinical research training, and expansion of basic science activities.

SUMMARY

The dental problems that face our public are great and important. In the aggregate, they contribute to invalidism, absenteeism, pain, and expense. Our attack on these problems is both fundamental and clinical. The millions of people who have never seen a dentist, the millions of others who face loss of teeth and serious mouth disorders, the handicapped children with facial deformities, look to dental research for answers.

The request of the National Institute of Dental Research for 1965 is $20,135,000. This will support an increase of $517,000 in research grants; $8,000 in fellowships; $232,000 in training; and $238,000 in direct operations.

This request for 1965 is distributed as follows:

Grants:	
Research	$9,415,000
Fellowships	1,199,000
Training	4,708,000
Subtotal, grants	15,322,000
Direct operations:	
Research	3,482,000
Collaborative studies	565,000
Review and approval of grants	554,000
Program direction	212,000
Subtotal, direct operations	4,813,000
Total, 1965 appropriation request	20,135,000

Dr. Arnold. With your permission, I would like to summarize it quickly and make some comments relative to progress.

Our full statement does present an overview of the research accomplishments which are the fruit of the continuing efforts of the Institute and grantee scientists that we are supporting to investigate the causes, prevention, and treatment of oral diseases.

CAUSE OF DENTAL DECAY

In the 15-year history of the Institute, we feel that we have achieved a considerable body of knowledge about the causation and prevention of dental decay, which, as you know, is one of the most prevalent of all of our diseases. We have recently established that tooth decay, at least in hamsters and rats, is a transmissible disease. I reported this to the committee last year. Today work is being carried forward into studies of the bacterial factors in human dental disease, so that control methods may be found for, particularly, the rampant caries cases. These represent the most virulent form of dental decay we have in our children.

Our current research has brought new understanding of the mechanisms of the action of fluorides, as our electron microscopy studies and X-ray diffraction studies have revealed that the fluorides render the crystals of bones and teeth more stable and less soluble in acids. The patterns of development of the dental enamel have also been studied through electron microscopy to review the mechanism of decay. The studies of flouridation of water supplies, with which this Institute has had a long association, have resulted, as you know, in steadily increasing use of this health measure.

PERIODONTAL DISEASE

Periodontal disease, the major adult dental disease, is a worldwide problem producing the loss of all teeth in a high proportion of the population over 45 years of age. Studies on the causes of periodontal disease have developed significant knowledge of the mineralization of bacteria to form calculus, the role of diet, and the correlation of the disease with states of poor oral hygiene. Most significant, we believe, is the discovery this year by Institute scientists that a condition very like human periodontal disease is, in hamsters, transmissible through bacterial processes. The identification of the micro-organism which produces the infection in animals does provide us with a lead to the conditions which may cause it in humans.

We have shown that a transitional form of bacteria resembling what are called the pleuropneumonia-like organisms, has been isolated from the oral tissues and the bloodstream of patients suffering from stubborn canker sores, which are extraordinarily resistant in some people and are very resistant to any treatment that we have today. I think all of us have suffered at times the pain of the canker sore. An understanding of the virus or the bacteria responsible for these and other similar oral ulcerations will, we believe, lead to a markedly improved method of therapy.

CLEFT PALATE

This year has brought new hope to the cleft palate patient. The Institute scientists have studied the mechanisms of speech, swallowing, and respiration in efforts to provide more effective guides to proper planning and timing of corrective surgery. Under grants from the Dental Institute, we have established two new centers for the study of cleft palate; thus bringing the number of such centers to six. These present wide-ranging research programs encompassing the surgical, orthodontic, prosthodontic, pediatric, psychiatric, and rehabilitative measures, as well as developmental and genetic factors, and provide the fundamental recourse for the 6,000 to 7,000 babies born each year with cleft palate.

As you are aware, Mr. Chairman, we have submitted a special report to the committee on progress in cleft palate and I would like to, with your permission, incorporate it in the record.

(The information referred to follows:)

Special Report—Cleft Palate Research

Cleft palate is a condition which develops in 1 out of every 750 babies born each year. In this country 6,000 to 7,000 infants each year enter life with cleft palate and may also have a cleft lip.

This birth anomaly presents a serious adjustment problem not only for the afflicted children, but for their families as well. Because the child lacks a solid surface between his tongue and nasal passages, he is confronted with problems affecting his facility to chew and swallow, his ability to speak and hear, and his emotional need to appear physically normal. His condition makes him susceptible to diseases of the ear, nose, and throat, and increases his need for dental treatment.

The adjustments his parents and family must face are not easy. They must learn how to feed their child so that he may get necessary nourishment; they must learn how to help him with his speech; they must learn patience with the tasks his cleft prevents him from performing as rapidly or adequately as unaffected children; they must learn to make him feel accepted and loved. The family must do all this despite the feelings of guilt and disappointment that so many experience. For without the encouragement and complete acceptance from the family, the child faces even further adjustment problems.

Obviously, cleft palate, a cause of great suffering, demands utmost scientific attention. Current research is extensive. The National Institute of Dental Research is conducting studies within its own investigative program and has granted funds for numerous studies in various academic and private research institutions throughout the United States and in several European countries. The newly established National Institute of Child Health and Human Development is also supporting numerous studies, particularly in the field of embryology and prenatal development. Also, the National Institute of Neurological Diseases and Blindness includes research and training pertinent to cleft palate and cleft lip in its major program responsibilities relating to disorders of speech and hearing.

These scientific studies are approaching the cleft palate problem through many scientific disciplines in order to find the reasons for its cause and to determine the best methods for its treatment. The ultimate research goal is, of course, prevention, and hopefully, once the causes are understood, prevention will be achieved. Research has given us a great deal of knowledge on the causes and treatment for cleft palate, but research at best has only skimmed the surface of the problem.

Not many years ago cleft palate was considered strictly the therapeutic domain of the surgeon. Operative procedures were improved to a point where the immediate repair appeared a success. Eating ability and physical appearance showed great improvement. However, in a few years, disfigured faces, underdeveloped jaws, distorted teeth, and awkward speech testified that the success was temporary. The surgeon was often unable to assure proper jaw development, tooth eruption, and a functioning palate.

From these results, it was clear to Dr. Herbert Cooper of the Lancaster Cleft Palate Clinic (Lancaster, Pa.) that a total approach to the problems of the cleft palate patient was in order. He proceeded to develop such an approach and in effect set up a model clinic. As a result, today's research effort embodies a multidisciplinary program in which teams of researchers from many different scientific areas pool their scientific talents and resources. These research efforts may focus on single problems such as palatal mechanisms or speech therapy, or they may range across broader fields of normal and pathologic study.

SOME CURRENT RESEARCH PROJECTS

Research within the Dental Institute has been undertaken on the mechanisms of swallowing in the newborn. Such a study seeks to explain basic questions on why and how this function is performed. This knowledge can then be related to the pattern of swallowing in the newborn infant with a cleft and when correction is attempted the surgeon will know how to operate without interfering with swallow function.

The physiological developmental pattern of the child is another important consideration in the correction of cleft palate if the treatment is to maintain its effectiveness. Studies on the rates and patterns of normal palatal growth and development have been undertaken so that investigators will be able to assess how the patient will continue to develop and what surgical techniques at what point will best promote his individual pattern.

Nutritional studies are underway to determine the role of diet in the growth and development of the fact. The application of this knowledge includes an understanding of how nutrition will influence facial growth in the cleft palate patient.

The chewing function in cleft palate cases is being studied to determine the influence of surgical treatment and of prosthetic appliances on chewing efficiency and swallowing. If chew-and-swallow efficiency is unnecessarily sacrificed, there is probably a decrease in the number and variety of beneficial foods that the patient can eat.

The physiological processes involved in speech are another significant aspect of the cleft palate problem. Growth functions of various structures involved in the speech processes are being studied to develop surgical and prosthetic procedures which will promote effective speech. Investigators are developing techniques to help the child learn to overcome speech deficiencies.

Study of the basic nature of speech to determine the relationship between the motor events of speeech production and the perceptual units of speech reception is underway. An understanding of normal speech production and its role in communication, knowledge of normal and abnormal patterns of articulation and development of new methods of therapy are proceeding at the same time.

Modern, often intricate instruments and a variety of scientific approaches are being used in cleft palate research, both for diagnosis and treatment. The instruments often represent important research achievements in themselves.

For example, cineradiography (another area in which the Lancaster Cleft Palate Center pioneered), the process of X-ray motion picture photography of soft tissues of the body, is being used to study the dynamics of speech and other oral functions. The slow motion pictures visible on a screen show the movements of the tongue, the jaws, and the throat during speech, breathing, and swallowing. This technique makes possible comparison between normal and surgically corrected functions of cleft palate patients, as well as function in the patient with uncorrected cleft palate. The pictures are projected slowly and can be stopped at any point for study, drawing, or diagrams.

Electromyograhic techniques are used to record patterns of muscular activity, such as the movements of facial and jaw muscles during the various oral and facial functions; i.e., eating, swallowing, breathing, chewing, and speaking.

Small pieces of metal are implanted at specific anatomic locations in order to observe positional changes of the jaw and face during development. Direction and amount of growth can be analyzed with this method and detailed studies of tooth movements during eruption can be carried out.

RECENT ADVANCES IN CORRECTIVE AND REHABILITATIVE PROCEDURES

Instruments used to measure hearing have revealed that there are significant differences in hearing difficulties among children with cleft palate and that these differences vary with age. These findings help to decide the age at which prosthetic correction can achieve maximum hearing efficiency and prevent hearing loss.

A useful device for feeding the infant with a cleft palate has been developed through the research efforts of creative scientists. Because of his palatal formation, the infant with a cleft cannot suckle. Liquids find their way into the nasal passages. In the past many infants with cleft palate suffered severe nutritional deficiencies and even starvation. The newly designed nursing bottle is J shaped, and is used with the baby in prone position, thus preventing airway obstruction and allowing patterns of motion of the tongue and lower jaw. This instrument, developed at the University of Utah, was recently improved at the Dental Institute.

Obturators and prosthetic appliances have been improved to help the process of chewing and other oral functions. Analysis of forces on natural teeth and bone structure is part of the program, because these studies are concerned with supporting tissue health. Great advance has been made in surgery and continues to be made. Age, types of correction, and followup are all included.

CAUSES OF CLEFT PALATE

Continued progress in cleft palate treatment is dependent on a better understanding of its basic causes, and an understanding of the basic causes, in turn, will hopefully lead the way toward prevention.

Obviously, the question, "Why does cleft palate occur?" has been answered only in part. Experimental investigations have turned up many exciting leads, but no definitive answers have been found. Investigators feel that in the final analysis the cause will not prove to be a single factor, but a complex of genetic, mechanical, chemical, nutritional, infectious, and metabolic factors which are either initiated prior to conception or which occur under the influence of the fetal environment.

Studies have shown that certain syndromes which sometimes include cleft palate can be attributed to a chromosomal anomaly. One extra chromosome present in a specific set causes widespread congenital anomalies severely affecting the oral-facial structures. Cleft palate frequently occurs in a chromosomal aberration in which a male child has three extra "female" chromosomes. Since the cases of cleft palate which can be definitely attributed to chromosomal anomalies are not numerous, scientists are seeking to determine whether or not a specific genetic configuration on the chromosome could predispose to cleft palate and account for the bulk of the cases.

In animal systems it has been found that specific conditions during gestation can lead to facial clefts. Excessive amounts of cortisone in mice, for example, definitely cause clefts in the offspring.

Anoxia (lack of sufficient amounts of oxygen), or folic acid deficiency, during pregnancy of experimental animals, will also produce cleft palate in their offspring. Investigators are studying the mechanisms of palate fusion and cellular differentiation in rat embroyos from folic acid-deficient and normal mothers.

In another investigation into the causes of cleft palate, the striking finding has been made that a specific chemical agent causing cleft palate also causes chromosomal changs. The fact that a drug, 6-aminonicotinamide, which changes the fetal environment can actually alter the chromosomal pattern in the body cells throws light on the "how" and "why" of cleft palate.

MULTIDISCIPLINARY CLEFT PALATE CENTERS

The ultimate goal of basic research into the causes of cleft palate will be to correlate the various findings on the affect of fetal environment and hereditary conditions in order to decide the factorial combinations in the development of the anomaly. The realization that cleft palate is a complex deformity caused by a multitude of factors and treatable only through consideration of a number of variables has initiated the impetus for multidisciplinary research centers.

Under this type of a program the individual is considered as a total person, not just a "swallow" problem or a "speech" problem. The ultimate goal is total rehabilitation of the patient. His emotional needs as well as his physiological requirements are carefully studied by a team of scientific specialists. Participating in these large-scale programs are surgeons, speech therapists, orthodontists, prosthodontists, pediatricians, psychologists, and social workers from diverse fields of clinical research; and embryologists, biochemists, geneticists, physiologists, and pathologists from vaccines basic research areas. This type of research approach is now being carried on in six centers under Dental Institute grants.

One multidisciplinary program is studying speech patterns in palatal cleft patients as a key to evaluating different treatment procedures. This team of scientists is conducting basic research on deformities of the mouth, clinical research in oral function, dental management, speech problems, and corrective surgery. Surgical, dental, and basic physiological studies are correlated and studied in terms of speech adequacy.

Another multidisciplinary program is concerned with the cause, functional activity, and therapeutic management of cleft lip and cleft palate. The program is coordinating scientific investigations in genetics, embryology and the mechanisms of clefts, and is evaluating treatment and psychosocial factors.

Cineradiographic films are being correlated with spectrographic patterns of sound in order to observe and analyze the dynamics of speech in cleft palate patients who wear a dental prosthetic speech aid. The investigators are endeavoring to determine the best location of the speech aid to produce optimal voice quality. The mechanisms of affected structures involved in the speech processes are evaluated as one phase of a long-range objective to establish a standard for each of the contributing factors in production of speech. In this study investigators are seeking the significance of each factor in normal speech and variations in abnormal speech. The collection of exact mathematical data on research findings is an important contribution to all disciplines concerned with cleft palate management, regardless of specialty training.

In another multidisciplinary program designed to develop maximum rehabilitation of cleft palate individuals, one can find surgery, longitudinal studies of hearing profiles, studies of emotional and social development, investigation of other anomalies in cleft palate patients, research in etiology and pathogenesis of clefts and other congenital anomalies, and development of criteria for use of prosthetic appliances. Currently the investigators are exploring utility of teleradiographic equipment in the diagnosis and treatment of human speech defects.

In a program geared toward a standardized method for the treatment of the cleft palate child, investigators representing a large number of disciplines will correlate growth and development of not only the maxillofacial area, but the whole individual as well.

A study to develop a surgical technique to prevent the defects of speech (nasality) associated with speech incompetency due to cleft palate is also being attacked through a multidisciplinary approach. Physiological factors involved in the movements of the speech structures are being studied in relation to their effect upon the transmission of air and sound energy within the vocal tract. Perceptual evaluations of the speech sounds produced are obtained so that the physiological and acoustical characteristics of normal and abnormal speech production can be interpreted.

MANPOWER AND TRAINING

One of the great problems in research today is manpower. Without trained specialists, no program, no matter how beautifully designed or how visionary the approach, can be effective.

The Dental Institute is supporting several training programs in the areas related to cleft palate research. Some are individual training programs where the student receives further education in his background specialty, while some are conferences designed for advanced training for specialists already active in the field.

As one example, physicians and dentists in private practice, including prosthodontists, plastic surgeons, pediatricians, psychologists, and speech and hearing therapists attended a 4-day lecture series in oral anatomy and physiology growth, and development patterns in the normal as well as cleft palate patient, and new surgical and dental treatment procedures.

BUDGETS FOR CLEFT PALATE RESEARCH

In fiscal 1963 the National Institute of Dental Research supported, through grants and training programs, and through its direct operations, activities in the field of cleft palate amounting to approximately $2½ million.

There were some 55 research projects in universities, clinics, and hospitals, carrying support of approximately $2 million. In addition, many projects in pathology, histology, cell biology, growth and development, etc., have application to the field of cleft palate and will, through their findings, materially benefit the cleft palate patient. However, these have not been included in our figures since their purposes are broader.

Approximately half a million dollars was provided for grants for research training in fields pertinent to cleft palate.

Early in fiscal year 1964, 17 research grants, mainly in growth and development, were transferred to the National Institute of Child Health and Human Development. This Institute is also funding several programs in the current fiscal year.

DENTAL TREATMENT PROCEDURES

Dr. Arnold. In the field of dental treatment procedures, we have seen a great change as a result of the high-speed drill and other new cutting devices which have revolutionized dental practice. Our research institute has shown that the use of appropriate coolants will avoid pulp damage. In other words, that is the damage to the vital parts inside of the tooth. Collaborative research programs are now seeking to develop filling materials which will bond to the tooth structure. I spoke to this point last year.

Approximately four-fifths of the Dental Institute's funds are allocated to research institutions for scientific investigations and for the training of future researchers. As of November, the Institute was supporting about 400 research projects in 129 universities, including all 50 of our dental schools.

MANPOWER

Today, as health emphases shift from the acute infections to the debilitating illnesses, we can expect more intense focus on the problems of oral disease and oral health. Manpower continues to be a problem with us. Training of dental scientists is one of our major goals at the present time. A new committee of advisors to the Dental Institute has been formed to try to plan and carry out a nationwide effort for development of increased research manpower.

The creation of dental research centers has moved forward. We have received letters stating their preliminary plans from eight universities. Two of these universities have already received awards of funds by the Division of Research Facilities and Resources for the construction of facilities. We have awarded two larger program-project grants to two institutions to establish research nuclei around which we can build a research institute or research science center.

In summary, this budget request for the Dental Institute for fiscal year 1965, is $20,135,000. This will support an increase of $517,000 in research grants; $8,000 in fellowships; $232,000 in training; and $238,000 in direct operations.

Now, if I may, Mr. Chairman, with your permission, make a few comments on some of the progress we have made during the past year or two in certain fields.

Mr. Fogarty. All right.

PROGRESS IN CLEFT PALATE ACTIVITIES

Dr. Arnold. I realize that you and your committee have been interested in the field of cleft palate.

Mr. Fogarty. We do not think you are doing enough.

Dr. Arnold. I recognize that and I agree with you, sir. I wish we could be doing more and I hope we can be doing more.

I feel, as you will recall my saying last year, that some of the problems of the Dental Institute are similar to the problems of the Mental Health Institute in the fact we are dealing with long chronic disease disorders. I am sure you recognize that, in cleft palate, we are dealing with a congenital malformation originally and with many implications later on in life.

I would like to emphasize that I believe we have made some progress in the past 5 to 10 years. I think that it may not be quite recognized that the establishment of these cleft palate research centers—which I said we had four of last year and two more this year—has meant progress, Mr. Chairman, because I would remind the committee that some 20 or 25 years ago, there was practically no research being done in the field of cleft palate. At that time, the cleft palate patient was the subject of treatment by the plastic surgeon who treated the child very early in life due to the complications of feeding, and due to the reaction of the parents demanding that the lip be closed and the palate be closed.

We have talked to this committee in the past and said that some of this early treatment had not proved to be truly beneficial. This caused the field of activity relative to the cleft palate patient to be centered on rehabilitation centers and not really in the field of research.

DENTAL RESEARCH CENTERS

Upon the advice of this committee and with funds appropriated by Congress, we have in the past 4 or 5 years been able to allocate some of our research funds to establish these categorical research centers.

Mr. Fogarty. Are you satisfied with the progress you have made in the past year?

The reason I asked, it seems to me that Dr. Shannon said in his statement that he was not overly happy with the progress that was made in the last year in the establishment of these centers, something along that line.

Maybe I am not quoting him correctly, but I think I remember him saying something along that line.

Dr. Sessom. It was his hope it would move forward more rapidly than it had.

Mr. Fogarty. That is probably the better way to express it.

Dr. Arnold. May I comment, Mr. Chairman? I think it is the semantics of this—I think we are using the term "centers" in about three different categories.

Mr. Fogarty. So let us talk about the category Dr. Shannon was talking to.

Dr. Arnold. I would like to.

Mr. Fogarty. All right.

Dr. Arnold. I would like to turn, first, to your question, have we made enough progress in cleft palate research?

Mr. Fogarty. I do not want to disturb your line of thought. Go right ahead.

CLEFT PALATE CENTERS

Dr. Arnold. I do not think we have made as much progress in establishing cleft palate centers as we might have. I think we have made very good progress in the last 4 or 5 years. They are expensive.

When I came to testify this year, I was looking over—I remembered your remark, Mr. Chairman, last year that you had heard us talk about cleft palate centers for some 10 or 12 years. To establish a cleft palate center requires, just for initiation, some $150,000 to, we will say, $300,000. When I took over as Director of the Institute, we were operating on a budget of $221,000, so we couldn't even establish one center at that time. Due to the graciousness and foresightedness of your committee, we now have funds in our grants program so that we have been able, in the last couple of years, to get some of these centers going.

I feel that this has brought, in addition to the plastic surgeon and the prosthodontist, the geneticist, and speech therapist and others to be involved in cleft palate treatment. I think we have made progress, but not that progress to which I can pinpoint and say, yes, we have a result here.

In our intramural program in Bethesda, we have confined our activities to, namely, two different areas. We have been studying the effect of the teratogenic agents in the production of clefts and other anomalies in experimental animals; a part of which was reported to you last year. I can say that we have, during the course of this last year, come up with a drug and a system whereby we can approach 100 percent production of clefts and other anomalies in the offspring of rats. If we get that done, then we can go back and test some of the factors that influence the production of clefts in utero.

On the other side of the picture, we have, in the course of the past 5 years, established a group that is studying the neurophysiology and neuroanatomy of not only the cleft palate but also of the normal patient; studies of the oral pharynx of the cleft palate and normal patient.

As a sidelight to this, during the past year or a little over a year ago, they developed a new nursing bottle for cleft palate patients. This sounds like a small gain, but then when one considers the number of years we have been trying to nurse and feed cleft palate patients with the ordinary old-fashioned nursing bottle, this has been progress. It has been progress made as a result of knowledge we gained in our neurophysiology studies related to where the sensory factors back in the throats of individuals are located. So that now, rather than lay the baby on its back or in the arms in a routine fashion, they are able to lay the baby on its stomach and feed it with a J-shaped nursing tube to prevent choking. This is just a practical result of some of the basic research studies that are going on but were not aimed at this purpose.

CLASSIFICATION OF CLEFT PALATE UNDER CRIPPLED CHILDREN'S PROGRAM

Mr. Fogarty. In cleft palates, could some of these expenses be borne by the crippled children's program of the Children's Bureau in the various States?

Dr. Arnold. The Children's Bureau is supporting some cleft palate rehabilitation centers. In the one I know about, funds go to a cleft palate rehabilitation center associated with the University of Illinois and their funds come from the crippled children's group through the State health department. These centers are more rehabilitation centers, Mr. Fogarty, than they are research centers.

Mr. Fogarty. You did not get my question. I am just wondering if the funds appropriated for the Children's Bureau and the crippled children's program could be used in the various States to take care of some of these problems of cleft palate in children?

Dr. Arnold. There is one use that we are making of those funds in this way, shall we say by supplementing or tying our activities in with those supported by such funds.

We are supporting some research projects in two places that come to my mind: The one I mentioned in Illinois where they are "adding on" research projects to their cleft palate treatment center; and the other area I can think of offhand is at the cleft palate clinic in Lancaster, Pa., which gets some support from crippled children's funds.

Mr. Fogarty. I guess you do not understand what I mean.

Let's take Rhode Island, for instance. When they have crippled children's funds turned back, maybe the doctor in charge might have said, "Well, I do not consider cleft palate to come under the crippled children's program."

What is your answer to that?

Dr. Arnold. I do not know that I can actually answer that.

Mr. Fogarty. I will ask it when the Children's Bureau appears before us anyway, but it seems to me this has happened in some States where the doctor in charge has made the decision that this does not come under the crippled children's program.

Dr. Arnold. I can answer it this way, Mr. Fogarty. I have been told that in some areas, the people running the crippled children's funds do not consider cleft palate in the same category as, shall I say, a clubbed foot or clubbed hand, and so forth, and it does not come out of those funds.

Mr. Fogarty. What do you think about it?

Dr. Arnold. I think it could, yes, and I think cleft palate is very definitely a problem of crippled children, because a child with a cleft is very definitely a crippled child.

Mr. FOGARTY. That answers my question.

All right, go ahead.

NEW DENTAL MATERIALS

Dr. ARNOLD. In the other areas of research that I might just briefly speak of, I did mention in this summary an area of increased effort in developing new dental materials. I mentioned this last year. This year, as you will notice in our budget, there is a "collaborative studies" line item for the first time, that is in our 1965 budget. It was included in our 1964 budget as a transfer.

These funds, Mr. Fogarty and members of the committee, are primarily to develop some of the newer plastic materials that have great potential as we see it for use as restorative materials, particularly in the anterior teeth of children and adults where the present filling or restorative materials are not nearly as successful as we would like to have them.

As an example, the average anterior filling will last about 3 to 4 years, and then has to be replaced. Well, it is expensive to begin with, and this is an expensive problem from the standpoint of shortage of dental manpower.

We have sought the advice of a special ad hoc committee in this area, which included people from very knowledgeable areas of plastic developments in this country, people who are nationally recognized in the field of surface chemistry, and a couple of people who are outstanding in the field of dental materials. They have come up with guidelines and we are proceeding with contracting with several profitmaking and not-for-profit research institutions in the country, because this is where the real know-how is in developing these plastic materials. We do not have that in the routine biological setups which you have in dental schools or in biological areas of health centers in our universities. Some of this work, of course, is being done in chemistry departments and engineering departments where we are encouraging some grants and getting those people to work in this area. So I think we have made progress in that field, particularly during this past year.

PROGRESS IN FIELD OF PERIODONTAL DISEASE

In the general field of periodontal disease, I think one of the interesting results that has come out from people at the Dental Institute, some of our scientists there who are working in the basic principles, is the fact that they have shown that there is a defect in the molecules of collagen in the connective tissues associated with a disease called lathyrism. Now, drug induced lathyrism has been used for many, many years to produce a pseudoperiodontal disease in experimental animals. It is a technique by which you can produce a destruction of the gum tissues and tissues surrounding the tooth.

The interesting feature in our findings in the laboratories in Bethesda has been that this change in the collagen factor that they have found may be the change that occurs in periodontal disease. It may be one of the early changes that occurs in the fibers which connect the tooth to the alveolar bone of the jaw. If this proves out, it is one lead from a basic laboratory standpoint that we feel is quite important.

Another result that has occurred in our laboratories has been to show that we have been able to produce by bacterial means periodontal disease in hamsters. Again, this gives us a laboratory model system by which we will be able to further our knowledge of this disease.

Mr. Denton. I did not understand that statement.

Dr. Arnold. During the past year, Mr. Denton, we have shown that in experimental animals—namely, the hamster—we have been able, by bacteria, by specific bacteria, to produce a periodontal lesion, periodontal-like disease. With this as a model system——

Mr. Denton. In their gums?

Dr. Arnold. In the gums and tissues surrounding the teeth in hamsters. This does give us now an experimental animal in which we can produce by specific means a certain type of periodontal disease; thus we can go ahead and study it. We know that bacteria are associated with periodontal disease in humans, too, but what bacteria and how they bring this about we do not know.

I think, Mr. Chairman, that covers it briefly—we have prepared some other material to expand on our periodontal disease program.

Mr. Fogarty. Submit that for the record then.

(The information follows:)

Special Report—Periodontal Disease

Periodontal disease is a destructive disorder of the soft tissue and bone which anchor the teeth. In people over 35, periodontal disease (known in its advanced stages as pyorrhea), is the most common cause of loss of teeth. Due to its effects, more than 50 percent of the American population over age 40 have lost one or more teeth, and two out of five persons have lost all of their teeth. It is estimated that more than 20 million people in the United States alone are in need of treatment for this serious ailment. They are threatened with premature and unnecessary loss of otherwise sound teeth.

In a typical community, almost the entire adult population and perhaps half the teenage population suffers from some form of periodontal disease. If the disease is not treated in an early stage, it advances as a destructive, slowly progressing, chronic process ending in deterioration of bone and loss of teeth.

Field studies in more than 25 countries have shown that this condition is a worldwide problem.

RESEARCH PROBLEM

At present, clinical management of periodontal disease is difficult, expensive and time consuming, and treatment represents at best a compromise, not complete success. The research goal is to clarify the cause, or causes, the best methods of treatment, and ultimately establish means of prevention.

A tooth is not cemented tightly in its socket, but is cushioned by a thin layer of tissue, the periodontal membrance, which lines the socket, and is anchored by tiny fibers embedded at the ends in the root of the tooth and in the bone of the socket. The periodontal membrane ("periodontal" meaning, literally, around the tooth), the gingiva, cementum, and the alveolar bone make up the periodontium. Researchers expect that careful analysis of the composition and metabolism of the periodontium will give important information about the initiation and progress of periodontal disease.

The white tensile fiber of the periodontal connective tissue consists chiefly of collagen, quantitatively the most abundant protein in the body and functionally one of the most important. Since connective tissues are the supporting and containing tissues of the body, it is clear that their study is of importance to many areas of medical science. In addition to the connective tissue diseases (including periodontal disease), processes like aging, wound healing, calcification, and bone resorption are dependent upon the special metabolic functions of connective tissue cells and the control mechanisms of these metabolic reactions.

The study of connective tissue involves the physiochemical properties of its constituents; the covalent, electrostatic, and hydrogen bonds which unite it; and the hormones, nutrition, infection and metabolites which may affect these bonds.

Research in periodontal disease thus involves biochemistry, microbiology, nutrition, enzymology, and many other disciplines.

CURRENT RESEARCH ACTIVITIES

Surveys of periodontal disease and possibly correlated factors have been made in populations of extremely varied ethnic and cultural backgrounds. Epidemiologists of the National Institute of Dental Research, in cooperation with the Interdepartmental Committee on Nutrition for National Defense, have made field studies with teams consisting of many scientists, including dental epidemiologists, nutritionists, and biochemists. The surveys reveal that in most population groups the onset of periodontal disease is early and that severe inflammation and advanced destruction of bone are present even in young individuals. Extremely high levels of periodontal disease have been documented in widely scattered areas: Lebanon, Trinidad, Vietnam, Thailand, and Burma. The epidemiological research indicated that periodontal disease is correlated with increasing age and lack of oral hygiene. It does not appear to be correlated with geography, fluoride levels in water, race, blood groupings, sex, molar attrition, blood analyses, socioeconomic factors, or nutritional status with respect to vitamin A, ascorbic acid, thiamine, riboflavin, and nicotinamide.

Scientists generally agree that deposits around the teeth, such as plaque (soft debris) and calculus (tartar), are the most important local etiologic agents for periodontal disease. However, there is little knowledge of the way in which this factor operates, or why some people form more calculus than others.

This year scientists at the Dental Institute demonstrated that in animals a form of periodontal disease is transmissible in nature. With a single type of micro-organism a periodontal disorder can be induced in hamsters which did not have the disease before. The causative organism has been identified as an aerobic, gram-positive, filamentous form of bacteria. This is a major step in evaluating the importance of the oral bacteria in the etiology of periodontal disease.

Grantees of the Institute have succeeded in establishing baseline data on the microbial composition of plaque and gingival crevice debris in humans, both in health and in disease.

At the same time, scientists have reported that oral bacteria mineralize to form dental calculus, but only the gram-negative bacteria and spirochetes contain lipopolysaccharide endotoxins which could account for the inflammatory phase of human periodontal disease.

In the study of the factors that influence the deposition of oral bacteria onto teeth and their subsequent mineralization into calculus, a model system has been introduced. Dialysis sacs containing sterile teeth and pure cultures of oral organisms have been implanted intraabdominally in rats. Rough concretions similar to dental calculus formed on the teeth implanted with micro-organisms. In contrast, teeth implanted without organisms became covered with only a fine, uniform precipitate. These investigations support the concept that dental calculus consists chiefly of mineralized bacterial deposits, and that no one oral organism shows a unique propensity to deposit on teeth or to mineralize.

In spite of the finding that in certain animals periodontal diseases has a microbiological basis, other scientists at the Dental Institute have observed that a strain of mice maintained under germ-free conditions can have a form of periodontal disease associated with calculus-like deposits on the teeth. Why this occurs in the absence of bacteria is unknown. Whether the two diseases are the same is unknown.

In other animal experiments, a finding that dental calculus cannot form when all the major salivary glands are removed has led to the hypothesis that whatever influence diet may have on dental calculus deposition, it is mediated through the major salivary glands after gastrointestinal adsorption of food. Even animals fed by intubation directly into the stomach formed calculus if salivary glands were present.

Since it has been shown that fluoride improves the crystallinity of bone and teeth, it has been speculated that fluoride ingestion might have some value for the prevention and treatment of periodontal disease. Preliminary studies in the Dental Institute indicate that fluoride ingestion may inhibit alveolar bone loss, a stage of periodontal disease.

Studies of connective tissue in the Dental Institute have shown that a change in the maturation of this substance may occur and this may provide a key to the mechanism of the disease process. Connective tissue function depends on the integrity of the physiochemical bonds that hold together the constituents of the tissues. What happens to these bonds is therefore an important field of study.

A recent investigation has shown that newly synthesized collagen undergoes a maturation process during which intramolecular covalent cross links unite polypeptide chains to build a collagen molecule. The process of linking continues, forming a stable matrix of fibers. In experimental animals, a disease called lathyrism can be induced. This is a disease of connective tissue and in it the processes of cross linking are interfered with. It would seem that this important physiological step in the formation of stable collagen matrices has some relation to the degeneration of collagen as it takes place in periodontal disease.

Histochemical methods can complement biochemical methods in the basic studies on the periodontium. Stains applied to sections of tissue under the microscope can delineate for the histochemist the site of broad classes of substances, such as proteins, mucopolysaccharides, cartilage, and bone. Sometimes the stains specifically locate substances such as the nucleic acids and enzymes within the cells. The search for more selective stains may help to identify the molecular changes that occur with periodontal disease. There has been some success in studying enzymatic activity of normal connective tissue and of chronically inflamed tissue. Much work has been done, and more needs to be done, to develop methods of preparation (demineralization) of hard tissue while retaining enzymatic activity

Institute grantees are studying the nature of contact between the gingival epithelium and the tooth enamel surface. They are concerned with basic studies on the physiochemical properties causing cells of the gingiva to adhere to the teeth. Investigations indicate that close contact between the gingiva and the teeth is important for the health of periodontal tissues and constitutes part of the picture of host resistance to periodontal disease.

Bacterial enzymes are being studied as possible factors in cellular attraction at the gum margin. An electron microscopic study of the penetration of microorganisms into tooth dentin and into adjacent periodontal tissues is underway.

Suppression of the bacterial components in periodontal infection is being attempted through the use of antibiotics and dietary control. Since the specific filamentous organism that was discovered to produce periodontal disease in hamsters seemed to differ significantly from all recognized species while it resembled a group of organisms isolated in varioues laboratories, a cooperative study of these bacteria is being undertaken by the Dental Institute, the PHS Communicable Disease Center, and the University of Wyoming.

Research by grantees is seeking to identify antibodies against the microbial enzymes which promote tissue degeneration. The possibility that the gingival tissues become allergic to one or more compounds in bacterial cells is also being explored.

The role of emotional tension and systemic disorders in diseases of the oral tissues is under investigation in several centers. It has been recognized that special methods of periodontal therapy are needed for persons suffering from such systemic diseases as diabetes and heart ailments. However, the oral physiological and biochemical changes which occur under stress or as result of disease need to be evaluated.

RESEARCH SUPPORT

As befits the most important oral disease afflicting our adult population, extensive research in periodontal disease is being conducted and supported by the National Institutes of Health. The great majority of research projects in periodontal disease are supported by the Dental Institute, including studies of preventive measures, causes, and treatment. In addition to some 25 research programs specifically related to periodontal disease problems, there are scores of Institute-supported studies on the oral mucosa, the bacteria of the oral cavity, the salivary glands, the destruction of hard tissue, the ultrastructure of mucosa and bone, nutrition, metabolism, protein synthesis, genetics, and other subjects which have a direct or indirect bearing upon our knowledge of periodontal disease.

All the laboratories and branches of the Dental Institute conduct research in basic aspects of periodontal disease and a proportionate amount of the Institute's direct operating budget is devoted to this purpose. Approximately 20 percent of the Institute's grants budget for research is expended for periodontal disease research. Some is directly clinical, some related to the basics of calculus formation, tissue change, bone change and environmental factors.

In November 1963 the National Advisory Dental Research Council went on record to recommend strengthening of research in this area. Toward this end, a conference of outstanding clinical and basic science investigators was suggested. The Council also recommended establishment of a study group to augment cross-fertilization of ideas among clinicians and basic scientists. A third suggestion was for the establishment of a center or institute for teaching and research in periodontal disease.

Periodontal disease at the present time is costing the American public more than a billion dollars a year, even though only a small part of the people needing treatment are receiving it. Research in periodontal disease obviously requires no more than a small fraction of this expenditure.

SPECIAL REPORT ON DENTAL RESTORATIVE MATERIALS

Mr. FOGARTY. Do you want to say anything more about dental materials? You have been doing quite a bit of work in that area, have you not? Or do you want to submit it for the record?

Dr. ARNOLD. I think I can do it more completely by what was being submitted to the record.

Mr. FOGARTY. All right, we will do it that way.

(The information follows:)

SPECIAL REPORT—DENTAL RESTORATIVE MATERIALS

INTRODUCTION

Dentists have been confronted for centuries with the problem of replacing missing tooth structures by artificial materials. Restorative dentistry (the filling and replacing of teeth) occupies the greatest proportion of the time of the practicing dentist; perhaps as much as 60 to 80 percent. Research into appropriate materials and technics is an important function of the National Institute of Dental Research.

Search for the most effective materials has been going on since the beginning of the dental art. Research into newer instrumentation is a more recent development, but today with advances in chemistry, physics, and engineering some progress is being made. The chief problem is to make correct practical application of the new information as a stepping stone to increased knowledge of a complex and difficult field.

The Dental Institute, as part of its broad objectives to conduct and support research on the causes, diagnosis, and treatment of oral and dental diseases, has pursued studies of the structural components of the oral and dental tissues, related physiologic and pathologic processes, and materials which can be used for dental repair.

Within the scope of these activities, the Dental Institute has assumed responsibility for studies in the restoration to physiological form and function of hard and soft oral and dental tissues lost or otherwise altered as a result of disease, trauma, or operative intervention. The Institute has also conducted and supported research in the development, modification, and biological evaluation of restorative materials and operative procedures.

RESEARCH AT THE DENTAL INSTITUTE

Investigations of biological responses to therapeutic and restorative procedures.—With the introduction of tungsten carbide burs and diamond stones shortly after World War II and the resulting emphasis on improved tooth cutting procedures, a number of instruments were developed using increasingly higher rotary speeds. In order to assess the clinical applicability of these newer instruments, controlled investigations were undertaken to determine the biological responses of dental tissues to the changed treatment procedures.

The clinical-pathological research carried on by the investigators of the Dental Institute today comprises the principal body of knowledge by which investigators throughout the world are able to standardize their interpretations of clinical and histopathological findings. On these studies are based current analyses of the effects of high-speed instrumentation, assessment of the responses of the dental pulp and periodontal tissues, the effectiveness of ultrasonic and airbrasive technics, and the use of restorative filling materials and therapeutic agents.

Additional studies have contributed in important measure to our knowledge of the action and efficacy of pulp capping agents, protective coolants for cutting procedures, and periodontal medicaments. These studies have been communicated to the profession in an important series of papers and through a technical exhibit, as well as presentation at scientific meetings.

The Institute also conducts collaborative studies with other groups, and particularly with the National Cancer Institute, in order to formulate principles for the design and fabrication of prosthetic devices needed in the reconstruction of the face when disease or injury has caused deformity.

Other studies have led to therapeutic procedures for the stabilization of teeth by amalgam splinting and parallel pin methods, and pressure appliances for post-surgical management of recurring soft tissue proliferations.

Investigations of the physical biology and chemistry of dental structures.—The Dental Research Section of the National Institutes of Health (predecessor to the Dental Institute) began in 1945 work on the physical biology of the hard dental tissues. This research has not only augmented basic knowledge of the microstructure and properties of the teeth and oral tissues, clarified our knowledge of disease processes (especially tooth decay), but has provided new information on all aspects of tooth structure from relatively gross details to complex atomic arrangements within the mineral component, and molecular interrelationships between organic and inorganic constituents.

As the years of work have progressed there has been increasing evidence of the importance and usefulness of the data accumulated through this biophysical approach. Electron microscopy and diffraction, microradiography and X-ray crystallography have given us increasingly detailed knowledge of the mechanisms of growth and development within the dental and oral tissues.

One of the primary conclusions of the Dental Institute's Committee on Adhesive Restorative Materials was that the formulation of a satisfactory material for tooth restoration would be based upon intimate knowledge of the fundamental structural and chemical properties of the biological substrates and the special characteristics of instrumentally repaired surfaces. The research program on calcified tissue structure in the Institute's Laboratory of Histology and Pathology is integrally linked to projects on therapeutic measures. The studies in the composition and crystalline reactivity of oral tissues, and the investigations of the nature and properties of the organic matrices underlying the mineral have led to the idea of developing restorative materials with certain molecular bondings to collagen.

RESEARCH UNDER GRANT SUPPORT

The Dental Institute has recognized since its inception that the support of research in the field of dental materials is an integral part of its mission. Not only is extensive research supported, but training programs have been developed in such areas as metallurgy, biophysics, physical and colloid chemistry, crystallography and other basic disciplines important to the development of the restorative dentistry field. Before these programs were developed, no graduate training of comparable type, oriented toward dentistry, existed. There has been a sixfold increase in funds awarded for research and training in these areas during the last 4 years.

In addition to the 41 research projects currently underway in dental restorative materials, support is provided for a broad spectrum of biological and physical studies which are of basic importance for future development in this field.

The National Advisory Dental Research Council, the Dental Study Section and other advisory groups have expressed concern for development of a restorative material which would bond to tooth structure. A workshop was held at the University of Indiana in 1961 to explore current knowledge and to establish recommendations for future research. Three vantage points were selected for consideration of the total broad program: tooth structure; principles of absorption and adhesion in an aqueous environment; and materials and test methods.

The conference pointed up critical areas where basic knowledge was deficient and established specific recommendations:

A. The need to obtain more knowledge of the instrumentality prepared surface structure, the organic and inorganic chemistry of enamel and dentin and a basis for development of an intimately bonding restorative material;

B. The need to study a number of resin systems for their bonding capabilities;

C. The need to determine whether actual chemical bonding is essential or whether the forces of adsorption and morphological configuration might be adequate for attaining the relationship desired between the tooth and the restoration;

D. The need for the development of improved standardized procedures for assessing adhesion, marginal penetration and strength of surface films.

NEW PROGRAMS

An outgrowth of the 1961 workshop was the establishment of an Advisory Committee on Dental Restorative Materials to plan, to implement recommendations, and to coordinate the Institute's expanding activities in this field. The Committee is aided by consultants in metallurgy, ceramics, solid state physics, and other specialties.

As a result of the Committee's efforts, a literature survey has been prepared covering inorganic polymers. Another publication is currently in preparation which will list minimum requirements in the materials field, and will describe the physical and biological test methods, the components of the tooth, and the characteristics of its cut surfaces.

Plans are also being developed to stimulate industry research in adhesive dental materials and to develop research centers which will work in the broad physical and biological sciences basic to restorative dentistry.

Evaluation of instrumentation procedures, dental materials, and therapeutic agents; oral tissue responses.—Baseline data have been established on the pulpal response to cavity preparation. Evaluation of other instrumentation procedures, dental materials, and therapeutic agents now involves the evaluation of air-bearing turbine handpieces, carbide burs and diamond stones; evaluation of the classic gold foil restoration; assessment of pulpal response to full crown preparatory procedures; consideration of the use of corticosteroids in pulpal responses to operative procedures and pathologic processes, as well as the pulpal responses to constituents of silicate cements and adhesive restorative materials. A histologic analysis is being made of the ability of reparative dentin to reduce pulpal response to cavity preparation.

In the treatment of supporting tissues of the teeth, materials are sought which can be used for removable partial and complete dentures. This is accompanied by a parallel program to assess possible changes in the mucous membranes of the mouth after the insertion of denture bases, and to assess the magnitude of alveolar bone resorption under denture materials.

Increased research emphasis is warranted for investigation into the use of implant dentures. The principle of the use of nonirritating metals has been tested and established in other surgical fields, but in dental surgery the use of these materials has not completely been tested. Tolerance of the materials, and the growth and repair of the tissues are still not known.

Research in the properties of restorative materials.—Increased attention is being given to the use of cavity varnishes and liners. The use of radioactive isotopes and of dye techniques shows that varnishes seem to provide only a partial seal. Long-term studies will be required in this subject.

The acrylic resins have provided color stability and are insoluble in saliva. However, they have poor dimensional stability. New techniques in the use of cavity liners or primers may make them more acceptable as filling materials.

Research is needed to evaluate mass spectometry as applied to the analysis of the outer surface layer of solids. Contracts are supporting experiments in the field, and dental application will be developed when the experiments are farther along.

Research is also required on rubbery polymers and their interaction with hydroxyapatite and powdered dental enamel in order to identify the most promising substances for restorations. Metallurgical studies of amalgam alloys and gold alloys are needed. The applicability to dentistry of fiber metallurgy, investigations of wettability, surface tension and surface activity of metallurgical, and studies of electrochemical effects in the mouth are needed. Several new epoxy resins may have importance for dentistry if they prove to have adhesion, ultraviolet resistance, and water resistance.

CONCLUSION

As a science, the field of restorative materials in dentistry is new, but as a part of the practice of dentistry it is old. The new developments are in the direction of the application of basic science knowledge to the materials and techniques, which are important to the dental care of every person. This is work of immediate practical importance in which each advance can be adopted quickly with communication of resultant findings.

TABLE I.—*NIDR extramural activities; Research projects*

Research area	Fiscal year 1959		Fiscal year 1960		Fiscal year 1961		Fiscal year 1962		Fiscal year 1963	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Hard tissue structure	6	$127,560	7	$174,810	7	$118,876	12	$598,321	12	$347,145
Metallic materials	2	25,527	3	34,305	5	30,084	6	98,506	7	158,197
Nonmetallic materials	1	3,800	3	13,369	3	12,959	5	31,978	4	38,712
Synthetic resins	2	11,755	2	8,705	4	43,364	4	36,625	4	79,051
Elastomers	1	6,842	1	16,014	1	23,517	1	23,517	2	26,091
Biological evaluation	3	16,481	3	10,235	5	18,780	5	49,093	9	152,201
Multicategorical	----	----	2	30,015	2	28,520	2	36,172	3	51,765
Total	15	191,965	21	287,453	27	276,100	35	874,212	41	853,162
Research training programs	2	46,578	3	146,824	3	192,380	6	305,983	16	665,171
Grand total	17	238,543	24	434,277	30	468,480	41	1,180,195	57	1,518,333

Mr. FOGARTY. The amount available for 1964 is $19,140,000, and the request for 1965 is $20,135,000, or an increase of $995,000.

RESERVE

You have a reserve of $26,000. This is a little over one-tenth of 1 percent of your appropriation.

No one can estimate your needs to that fine a point, can he?

Dr. ARNOLD. No, sir; I do not think so.

Mr. FOGARTY. That is getting down pretty close. What happened? Did someone just decide he was going to establish a reserve and could not find the reasons to, so he just pulled this one out of a hat?

Dr. ARNOLD. I think this occurred a little differently than that, Mr. Chairman. This represents the unprogramed reserve which resulted from the reduction in general research support grants by the Bureau of the Budget after we had turned in our apportionments, and so forth. This was the amount allocated as the reserve in the Dental Institute. In addition, as I recall, there was some $82,000 reduction in general research grants, and we used a part of that to cover our increase in commissioned officers' pay but the $26,000 had not been programed.

DENTAL RESEARCH INSTITUTES

Mr. FOGARTY. Most of your increase is for research grants. Of the increase, $300,000 is for clinical research centers. Is this part of a plan to build up some dental research institutes as this committee indicated should be done in our report last year?

Remember last year, you really got a helping hand from Dr. Shannon along these lines. But this is what he said this year, so you can comment on it:

> With respect to the Dental Research Institute program, I note that here, too, the key to program initiation is construction funds. Dr. Stone has been cooperating with Dr. Arnold, Director of the National Institute of Dental Research, to assure that health research facilities funds are available to support this effort. I may say that so far, with this program, we have not aroused the degree of interest in the specific quarters that we had hoped for. The intent, as you will recall, is not merely to add an extra dimension to existing dental efforts—though this is not precluded per se; the real hope is to focus multidisciplinary scientific interest on the full range of dental problems, much as is done in NIDR itself. This could be accomplished, I feel, in any major university with strong biomedical research departments.

Dr. ARNOLD. Yes.

Mr. FOGARTY. Go ahead and say what you want to say.

Dr. ARNOLD. I am sorry, I forgot to speak to that after what you said a while ago. I will speak to it now.

I am in full agreement with what Dr. Shannon said there. We have, as he noted, given special priority for construction money in two universities, which are planning to go ahead with developing research centers and possibly institutes in that concept.

I think it should be pointed out to the committee and for the record that Dr. Shannon, when he was testifying to this last year, gave testimony with which I assisted and with which I agreed. We are talking about a concept of a development of research in large university centers, something that dentistry does not have today. Dental research has relatively small scattered nuclei. In some places, it represents two or three men in a dental school, some larger than that. But what Dr. Shannon was talking to and what bothers us, myself and other people who are working on planning for the Dental Institute, is that we have to create some type of environment to bring in nondental people, basic scientists, from other areas.

Mr. Fogarty. That is what Dr. Shannon was referring to?

Dr. Arnold. This is what he is referring to.

Mr. Fogarty. So it has not progressed as fast as you thought it would.

What about 1965? What are your hopes or what are your plans?

Dr. Arnold. We have been in negotiation with several institutions, universities, in this country during the course of this year and I think in 1965 we may make some overt moves along this line.

I would like to point out, as Dr. Shannon did, and referred to I think or alluded to, that after this announcement and after the record was out, I can assure you almost half the dental school deans talked to me about starting a dental institute or dental science center in their respective school or university.

I do not think this is quite the concept we are thinking of. We were thinking of larger centers or institutes—unfortunately, the words get mixed up—whereby we would have large nuclei and large groups to attract real strong, basic science people.

The proposals that we have had on hand are more in the realm of what he said were not precluded; that is, just to expand the program that you have. We are trying to expand this program in a broader way. We have even talked in areas where they do not have the traditional dental school, where you get into other factors of department jealousies, and so forth, and who is going ahead and where.

So I am hopeful, Mr. Chairman, that we may get someone interested.

RESEARCH GRANT PROGRAM

Mr. Fogarty. Now with regard to your regular research grant program, you are requesting just enough to carry forward at the same level of 348 pojects that you have in 1964.

Dr. Arnold. That is correct, sir.

Mr. Fogarty. I thought there was need for more research than the present level. This is a problem we have been hearing about for the last 2 or 3 years. Now you are leveling off.

Dr. Arnold. There is need. As expressed by grants on hand, we could be supporting more than 348 projects.

Mr. Fogarty. Do you have the people?

Dr. Arnold. If approved grants on hand represent having the people, yes.

Mr. Fogarty. How many more approved grants could you finance if you had the funds?

Dr. Arnold. The most direct answer I can give to your question, Mr. Fogarty, is that on our best estimate as of today—and we are approaching, as you know, the Council meeting next week—we will have about $750,000 worth of approved grants that we will not be able to fund in 1964.

Mr. Fogarty. Why do these councils not meet in January instead of March or April so that you can have their latest figures before you have to appear before this committee? I am not talking just about dental, I am talking about all of the councils that meet later on.

FELLOWSHIPS AND TRAINING GRANTS

Now, you have no increase in the number of fellowships you expect to support and you will have almost no increase in your training program, from 89 grants to 93. I was led to believe there was a real shortage of trained personnel in this field.

Dr. ARNOLD. There is.

Mr. FOGARTY. Yet there is no increase here at all to speak of.

Dr. ARNOLD. There is, Mr. Chairman, a shortage of scientific manpower.

Mr. FOGARTY. I assumed you asked for more than what is in this budget.

Dr. ARNOLD. Yes, sir.

Mr. FOGARTY. Those tables are all going to be put in the record, but do you want to say anything about them—what you asked the Department for, what the Department asked the Budget for, and so on.

Dr. ARNOLD. Well, in our preliminary request to the Department for 1965, we did ask for increases in research grants and in fellowships and a slight increase in the training program. This was not allowed by the Department or the Bureau of the Budget.

PRESIDENT'S HEALTH MESSAGE

Mr. FOGARTY. Were the dentists mentioned in the President's health message in any way at all? Dental health or dentists?

Dr. ARNOLD. To the best of my knowledge, no.

Mr. FOGARTY. I read it a couple of times. I do not remember seeing any reference made to dentists or to dental health.

Dr. ARNOLD. Mr. Kennedy did.

Mr. FOGARTY. Oh, yes, I thought Mr. Kennedy's message was one of the best ever delivered by a President. But I do not remember President Johnson referring to dental health or dentists at all; do you?

Dr. ARNOLD. I do not recall that he separated out——

RECENT AWARDS TO THE INSTITUTE DIRECTOR

Mr. FOGARTY. I do not have any more questions, although I would like to bring to the attention of the committee that Dr. Arnold received the William John Gies Award by the American College of Dentists at its annual meeting in Atlantic City on October 13. The award was given to Dr. Arnold in recognition of his distinguished career as a scientist and research administrator, and for his contributions to dental research and public health.

Doctor, the committee would like to congratulate you on receiving this honor. It is one well deserved.

Dr. ARNOLD. Thank you.

Mr. FOGARTY. It has also been brought to the attention of the committee that you received the 1963 Callahan Award by the Ohio State Dental Association in Cleveland on September 23. This award is the highest honor granted by the association for professional contributions to the art and science of dentistry and is presented annually to a person who has made a contribution of exceptional value to dental science.

The award was given for Dr. Arnold's work on fluorides and their effect on teeth and his extensive reports on oral bacteriology, oral pathology, and the epidemiology of dental caries.

The committee would also like to congratulate you on receiving this award.

Dr. ARNOLD. Thank you, sir.

Mr. FOGARTY. Mr. Denton.

Mr. DENTON. I would like to join Mr. Fogarty in congratulations, Doctor. I am sure the whole committee joins us in that.

PERIODONTAL DISEASE

Would you describe for me or give a definition of what periodontal disease is?

Dr. ARNOLD. In common language it is often better known as pyorrhea.

Mr. DENTON. All right; now I know.

Dr. ARNOLD. I would like to comment, Mr. Denton. Periodontal disease is a broader term than pyorrhea. Pyorrhea is an old term describing flowing pus. That is the late stage of periodontal disease.

FLUORIDATION

Mr. DENTON. You are having a great deal more success with the fluoridation program than you have had for a great many years, are you not?

Dr. ARNOLD. Yes; I do not know whether Dr. Galagan, when he testified for the Division of Dental Public Health and Resources, testified to this or not.

This is administered under the Division of Dental Public Health. Of course we are interested in the progress. There has been a significant increase in the number of communities which, during this past year or so, have, by referendum or otherwise, instigated or initiated fluoridation for caries control.

CAUSE OF CANKER SORES

Mr. DENTON. I did not understand your statement on what caused canker sore. Would you explain that a little bit more?

Dr. ARNOLD. I am not sure I explained what caused canker sores, because we have not known, Mr. Denton, what causes canker sores. But for the first time, we have been able to demonstrate a bacteria that is consistently present in different forms—as I said, it could resemble the pleuropneumonialike form of bacteria. They have demonstrated these in the tissues at the site of canker sores and also have identified antigens in the bloodstreams for——

Mr. DENTON. Most any sore of that kind is caused by some kind of bacteria, is it not?

Dr. ARNOLD. Bacteria or virus is often the cause of one of these. Irritation or stress is associated with oncoming of canker sores in people who are prone to them. Apparently there is a latent stage and this is what is important about these bacteria, because they show a latent stage form in the areas before the canker sore itself ever comes. Maybe if they are there, an irritation may elicit it as the ulcer in the mouth.

TOOTHPASTE PREFERENCE

Mr. DENTON. Now, we see so many ads about toothpaste preventing tooth decay. There is a great deal over the television.

Is there any preference that the dental profession has toward using different kinds of toothpaste? Or would you rather not answer that?

Dr. ARNOLD. No; I am trying to think.

Yes, I would say, as a whole, the dental profession has recognized that particularly some of the stannous-fluoride-containing toothpastes have shown to be of some benefit. The benefit probably—and I am more expressing my opinion now, Mr. Denton, than scientific knowledge—a toothpaste probably has its greatest value in its capabilities of oral hygiene, and so forth. But there is evidence, scientific evidence, to show that some of the stannous fluoride toothpastes do reduce to some degree the amount of dental cavities.

Mr. DENTON. That is all.

Mr. FOGARTY. Mr. Lesinski.

CAUSE OF CANKER SORES

Mr. LESINSKI. You mentioned to Mr. Denton that canker sores are caused by various germs, etc. Are not canker sores caused by disorder of the stomach?

Dr. ARNOLD. No, Mr. Lesinski; I think the picture is more like I said to Mr. Denton; there are certain types of stress that elicit the canker sores. In some people, they become quite severe. They are like an allergy, you might say. But we do not know an etiological agent, or have not. The hope that I was speaking of here is that we have found an etiological agent which may lie very dormant for years and then, on certain stresses become active. One of the things that is known is that the menstrual period in females will increase canker sores in those people who have the tendency. The question is, is the bacteria or the virus lying there in the tissue and that it takes the stress to bring it out and give you the ulcer which you realize is the soreness in your mouth and recognize as a canker sore?

Mr. LESINSKI. It is conjecture, trying to prove the point; yes or no? It is conjecture? In other words, you are trying to find out whether——

Dr. ARNOLD. We are trying to find out what is the cause and if such a thing could be the cause, Mr. Lesinski; particularly in those cases that I have seen where it is so severe they cannot eat, and their whole mouth becomes a canker sore—even back in their throat. Then the potentialities of therapy or of a vaccine or something are there.

USE OF FLUORIDES

Mr. LESINSKI. It has been a proven fact that fluoride used in water to prevent dental caries in the teeth cause poisoning. You prefer poisoning the body by drinking water than putting it on the teeth?

Dr. Arnold. Mr. Lesinski, I certainly would not advise fluoridation of water supply if I thought it in any way had any potentiality of poisoning the body.

Mr. Lesinski. Well, I am not going to get in an argument, but some day you will recognize the fact that it is so.

Is not gingivitis pyorrhea?

Dr. Arnold. Gingivitis is probably the first stage of pyorrhea, yes, sir.

CLEFT PALATE

Mr. Lesinski. I just want to say that you are attempting to do a proper thing, especially with cleft palate. Is there any proof it is hereditary?

Dr. Arnold. It has not been proven to be hereditary, but let's look at it this way: there are certain features of cleft palate that have a genetic type of background, thus certain types of cleft palate are hereditary.

Mr. Lesinski. Is not cleft palate the lack of roof of the mouth or proper development of the roof of the mouth?

Dr. Arnold. Correct. Or of the lip. It is a lack of development of the premaxilla bone—nasal—and it has degrees of extension, sometimes all the way from the lips right straight back through the mouth; sometimes just at the posterior part of the mouth.

Mr. Lesinski. It is quite an experience when one has a personal close associate with that problem and I am quite concerned. There have been quite a number of operations in this particular person's mouth and there has been no correction whatsoever. It seems nothing can be done at the present time. It is a very difficult thing to cure. I hope something can be done.

How far have you gone?

Dr. Arnold. I think we have improved greatly the techniques for treating cleft palate after it has occurred.

Our big problem now is to learn a little bit more about why it occurs. I mean where does heredity fit into this picture? Where does intrauterine environment change this picture?

Mr. Lesinski. Have you gone into the study of trying to correct it?

Dr. Arnold. Of what?

Mr. Lesinski. To correct it.

Dr. Arnold. We have several studies and a couple of these centers I spoke of are concentrating on better methods of correcting it.

To correct the cleft palate really requires plastic surgery. There is a lot of work in two or three of these centers that is concentrating on correlating the surgery with the movement and growth of the palate itself.

You cannot reconstruct what was not there. Because of the hole in the cleft, there is no tissue there, so you have to use a plastic means by which to replace it.

To finish, there are prosthetic appliances, too, that have been worked on to close the hole between your nose and your mouth which the cleft creates.

Mr. Lesinski. No further questions.

Thank you, Doctor.

Mr. Fogarty. Thank you, Doctor.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

WITNESSES

DR. G. DONALD WHEDON, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

DR. STUART M. SESSOMS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DONALD F. BROWN, BUDGET OFFICER, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

LOYAL FISHER, DEPUTY DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
11 Personnel compensation:			
Permanent positions	4,243	4,626	5,008
Positions other than permanent	147	150	150
Other personnel compensation	67	104	91
Totel personnel compensation	4,457	4,880	5,249
12 Personnel benefits	479	512	548
21 Travel and transportation of persons	284	366	360
22 Transportation of things	59	58	58
23 Rent, communications, and utilities	95	98	98
24 Printing and reproduction	17	57	57
25 Other services	933	1,717	1,559
Payments to National Institutes of Health management fund	5,070	5,474	5,719
26 Supplies and materials	915	930	916
31 Equipment	721	708	700
41 Grants, subsidies, and contributions	82,100	91,443	97,930
Subtotal	95,129	106,243	113,194
Deduct quarters and subsistence charges	18	18	18
Total obligations	95,111	106,225	113,176

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	653	654	669
Full-time equivalent positions	26	26	26
Average number of all employees	569	591	612
Employees in permanent positions, end of year	547	558	573
Employees in other positions, end of year	29	9	9
Average GS grade	8.3	8.3	8.3
Average GS salary	$7,688	$8,140	$8,095

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(a) Research	66,210	74,244	80,261
(b) Fellowships	3,924	3,979	3,979
(c) Training	11,966	13,220	13,690
Total, grants	82,100	91,443	97,930
2. Direct operations:			
(a) Research	10,602	11,490	11,867
(b) Collaborative studies	645	1,594	1,597
(c) Review and approval of grants	1,273	1,415	1,491
(d) Program direction	280	283	291
	12,800	14,782	15,246
Total program costs, funded [1]	94,900	106,225	113,176
Change in selected resources [2]	211	--------	--------
Total obligations	95,111	106,225	113,176
Financing:			
Comparative transfers to other accounts	404	--------	--------
Unobligated balance lapsing	7,873	1,474	--------
New obligational authority	103,388	107,699	113,176
New obligational authority:			
Appropriation	103,388	113,679	113,176
Transferred to "National Institute of Child Health and Human Development" (76 Stat. 1072–1074)	--------	−5,980	--------
Appropriation (adjusted)	103,388	107,699	113,176

[1] Includes capital outlay as follows: 1963, $482,000; 1964, $708,000; 1965, $700,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $542,000 (1963 adjustments. —$10,000); 1963, $744,000; 1964, $744,000; 1965, $744,000.

Mr. Fogarty. Dr. Whedon, we will try to finish with you and then we will come back in the afternoon.

General Statement

We will put your complete statement in the record and you can summarize it.

(The prepared statement follows:)

Mr. Chairman and members of the committee, I am pleased to report that the year which has passed since my last appearance before the members of this committee to discuss the program of the National Institute of Arthritis and Metabolic Diseases has been productive and rewarding.

I would like to tell you some of the encouraging developments both in the laboratory and in the clinic which have occurred during the past 12 months, and to describe them in relation to background, present situation and outlook.

RHEUMATOID ARTHRITIS

Some background is necessary to understand the present situation in the field of arthritis and the rheumatic diseases. Research in rheumatoid arthritis and the other rheumatic diseases has come a long way since 1948, the year in which the discovery of cortisone marked a striking advance in a stagnant area of research. In the following years, a series of advances were reported by research workers in the arthritis field. We learned of other new antiarthritic drugs, and of new blood tests for the disease, among other findings. We were told about the discovery of the rheumatoid factor, an antibody found in the blood of many patients with rheumatoid arthritis. This rheumatoid factor was an early clue which led us to believe that rheumatoid arthritis may be the result of an autoimmune reaction.

Immunity is one of the body's protective mechanisms against foreign substances. The term "autoimmunity" implies that the body fails to recognize one or more of its own tissue components as "native" and reacts to them as if they were foreign. This fresh concept of the possible cause of rheumatoid arthritis has gained support as more evidence has been gathered. We now believe that certain diseases, such as systemic lupus erythematosus, certain forms of thyroiditis and kidney disease, pernicious and hemolytic anemias and myasthenia gravis, may have an autoimmune component. Certainly this theory of autoimmunity has not yet been proven, but there is much evidence to support it.

Rheumatoid arthritis and environment

Another area of inquiry concerns the possible factors involved in the causation of rheumatoid arthritis through epidemiological studies, a tool which may clarify the respective roles played by environment and heredity. Last year I reported to you some preliminary results of a population study conducted by Institute scientists as part of a program designed to ascertain if heredity plays a role in the causation of rheumatoid arthritis and if populations living under different geographic and climatic conditions differ in the frequency of the disease.

Two tribes of American Indians living under extremely contrasting climatic conditions were selected and carefully surveyed. They are the Blackfeet of northern Montana, who inhabit one of the coldest areas, and the Pima of southern Arizona, who live in one of the warmest areas of the country. The members of these tribes have spent virtually their entire lives on their respective reservations which are their ancestral tribal homes, and hence should reflect any possible environmental influence on the occurrence of the disease to a far greater extent than most other population groups.

The NIAMD scientists' findings appear to indicate that the occurrence of rheumatoid arthritis is not tied to hereditary factors but may well be influenced by environmental factors other than climate. The prevalence of both rheumatoid arthritis and rheumatoid factor in both tribes showed a decidedly random pattern, uninfluenced by blood relationships, and was much higher in the Pima Indians than in the Blackfeet.

Other clues to the etiology of rheumatoid arthritis

Recent experiments by an Institute-supported scientist and other investigators have yielded information which may be interpreted to mean that certain rheumatic diseases may have been induced by infections with viruses or pleuropneumonia-like organisms. The rheumatoid factors resemble antibodies in many respects. They are presumed to be elaborated in the body in "defensive" response to abnormal alterations in the individual's own gamma globulins (a fraction of blood proteins), which, once altered, are now treated by the body like a foreign protein. That such a hypothetical alteration could be virus-induced has been implied by recent studies by Institute-supported scientists of the immune mechanism of the Aleutian mink. In Aleutian mink disease the animal develops a blood substance similar to the rheumatoid factor. The investigators have recently found that certain filterable substances transmit the disease and initiate the characteristic pathologic changes in mink tissues. These alterations resemble the changes seen in certain human rheumatic connective tissue diseases. Since this disease of mink is believed to be of viral etiology, the fact that it stimulates some of the rheumatic diseases of man raises speculation as to the possibility that similar causative mechanisms may be involved in certain of the human rheumatic diseases.

Rheumatoid arthritis—Clinical studies

Mention of laboratory research and epidemiological field studies in rheumatoid arthritis should not overshadow studies in the clinic where research is devoted to developing new methods of physical therapy and rehabilitation and to evaluating new antiinflammatory and analgesic drugs. Insight into the mechanism of action of antirheumatic drugs is beginning to replace empiricism. A better understanding of the basis for toxic reactions of these drugs is replacing resignation with therapeutic resourcefulness; the practitioner now knows how to prevent, reduce or overcome some of these noxious effects. Gold salts have maintained a position of high priority on the list of effective therapeutic agents in rheumatoid arthritis for the past 35 years. How or why they worked was a mystery—until this year. Now it has been demonstrated by Institute grantees that gold salts enter the large phagocytic white blood cells (macrophages) and inhibit the action of a family of important enzymes responsible for inflammatory reactions. Moreover gold salts have been shown to inhibit the production of certain antibodies. This promising line of investigation has only begun. It remains to be determined whether gold salts in low therapeutic concentrations inhibit immune responsiveness in man as well as in the test tube and whether synthesis of the rheumatoid factor as well as that of simpler antibodies is significantly suppressed.

In a significant proportion of patients, prolonged use of gold salt therapy results in undesirable toxic symptoms connected with retention of the gold compounds in the body. Recent studies supported by the Institute have led to the finding that penicillamine, a heavy metal-binding compound, sequesters gold salts deposited in tissues and enhances urinary excretion of the metal from the body. The future use of penicillamine in conjunction with gold salt injection therapy in rheumatoid arthritis may reduce the toxicity currently connected with this treatment.

Scientists supported by the Institute have found that a large dose of corticosteroid drugs administered every 48 hours will result in less serious side effects than heretofore associated with their conventional mode of administration in multiple, small divided daily dosages. This new mode of administration reduces the undesirable suppression of the adrenal gland, the incidence of peptic ulcers, psychotic reactions, and infections, which in many cases accompany the use of corticosteroid drugs, and with no loss of therapeutic efficacy.

Studies supported by the Institute, directed and supervised by the American Rheumatism Association and being carried out by the coordinated arthritis clinics in the country, have confirmed the efficacy of antimalarial drugs (chloroquin and hydroxychloroquin)in the treatment of rheumatoid arthritis. They are also useful in the treatment of systemic lupus erythematosus. Undesirable side effects are directed mainly at two structures in the eye, cornea and retina. The toxic effects on the cornea are reversible but not those on the retina. Fortunately, however, retinopathy is very rare. It is estimated that it occurs in less than 1 per 1,000 patients receiving prolonged therapy. Judicious and repeated ophthalmologic examination of patients receiving these drugs can detect undesirable effects early enough to avoid serious permanent damage.

GOUT

Last year I reported to you that we might now look upon gout as a form of arthritis, therapeutic control of which has progressively yielded to a relentless research attack. Almost all of the research workers engaged in this attack are Institute scientists or Institute-supported grantees. During the past year, Institute grantees have demonstrated that a new compound effecively inhibits uric acid synthesis which is excessive in gouty patients, thus markedly reducing uric acid in blood and urine. The drug appears to be well tolerated, thus adding another effective weapon to our armamentarium in the treatment of this form of arthritis.

Gout is known to be caused by a defect in body chemistry, which leads to an accumulation of uric acid in the body, a deposition of uric acid crystals in certain joints, and to periodic painful attacks of gouty arthritis. Past attempts to control the abnormally high rate of uric acid synthesis in gout by use of certain inhibitory agents have shown these agents to be too toxic for general clinical use. Although two of every three gouty patients today can be maintained with normal blood uric acid levels by the use of uricosuric drugs (drugs which enhance the elimination of excess uric acid via the urine), certain undesirable side effects stem directly from the increased urinary excretion of uric acid, such as renal stones and urinary sludge.

The grantees I mentioned have now reported results of a study of 15 gouty patients who were treated with the new drug hydroxypyrazolopyramidine (HPP). There were dramatic reductions of both serum uric acid levels and urinary uric acid levels in all patients, and no evidence of serious toxic effects. For the first time in the long history of this disease—described by Hippocrates more than 23 centuries ago—a successful attack has been launched at the origin of excessive uric acid production. A new and very significant dimension has been added to the treatment of primary gout.

Pseudogout, a new clinical entity

This past year Institute grantees have clarified the clinical nature and pathogenesis of "pseudogout," a recently identified member of the arthitis family.

A 3-year study by NIAMD grantees of 30 patients with a gout-like syndrome (previously diagnosed as suffering from gout, osteoarthritis, or rheumatoid arthritis) has revealed that this diathesis, although clinically resembling other arthritic diseases including gout, stands recognizably apart from them and constitutes a unique disease entity. Pseudogout is a crystal-induced inflammation of joints which often results in acute, painful arthritis. It is characterized by the presence of calcium pyrophosphate crystals in the articular cartilage and fluid of the affected joints, in contrast to gouty arthritis in which uric acid crystals are present in the affected joints. Studies are underway currently to elucidate the causes underlying this newly defined disorder.

DIABETES

During the past few years, diabetes research has witnessed a significant advance in knowledge, and application of this knowledge toward improving the health and life expectancy of diabetes patients. These advances, constituting one of the more hopeful pictures in contemporary medical history, are especially significant in the light of recent statistics released by the American Diabetes Association, which forcefully bring to mind the widespread occurrence of this disease and its much underestimated impact on our population. It is now estimated that there are approximately 3 million diabetics in our country. Moreover, about 5,125,000 other persons living today in the United States are potential diabetics, who will develop the disease sometime during their lives.

As I described to you last year, this best known of the metabolic diseases appears to result from insufficient insulin production by the pancreas, from antagonism to insulin in the circulation, or from an impairment in insulin action in the individual's tissues. I also reviewed the advent of the oral drugs which have replaced daily insulin injections in about one-third of the Nation's diabetics, and mentioned the evolving concept of "prediabetes." This year I wish to report continuing important findings in studies on oral drugs and of the prediabetic state, as well as other developments in the laboratory and in the clinic.

Synthesis of insulin

Perhaps the most significant finding, this past year, in the field of diabetes has been the synthesis by NIAMD grantees of a biologically active, artificial insulin molecule. Although its activity is at present far less than that of natural insulin derived from animal sources, this preparation will be an invaluable research tool for studying the mechanism of insulin action in diabetes. Moreover, this synthesis is an important step toward the eventual production of synthetic insulin for possible therapeutic use by injection.

The treatment of all cases of juvenile diabetes and of severe adult diabetes would be impossible without the daily administration of insulin. This hormone is presently obtained from the pancreas gland of various animals. In some diabetic patients it acts as an antigen, producing an undesirable "defensive," immune response which may severely reduce its therapeutic effectiveness. The present work opens the way to the synthesis of a pure, "nonantigenic" insulin molecule or of related manmade analogs which are therapeutically effective. Since the structure of insulin is complex, the recent successful synthesis required a highly sophisticated chemical process and was a triumph of fundamental laboratory research.

Improved diagnosis of diabetes

Methods and means to detect diabetes continue to be improved. For example, for many years a major laboratory tool for establishing the diagnosis of mild diabetes has been the oral glucose tolerance test. Although valuable, this test involves many variables in its performance and in interpretation of its results. During the past year, Institute grantees succeeded in developing a new diabetes screening test, the oral tolbutamide-glucose tolerance test, the accuracy, simplicity, and minimal side effects of which have warranted its inclusion among the diagnostic aids now used for the detection of diabetes.

In a related study, Institute grantees have found that response to glucose tolerance tests is affected by the periodicity of eating during the days preceding the test. In other words, whether an individual nibbles his food over a period of time or gorges himself on the same food at one sitting, markedly affects the results of subsequent glucose tolerance tests to detect diabetes. Nibblers have been found to display a definite increase in tolerance to carbohydrates, as determined by the tests, whereas gorgers may appear to be diabetic by the same criteria. Not only should these factors be taken into account in employing and interpreting glucose tolerance tests in the detection of diabetes, but this work introduces a new approach in the investigation of the relationship between man's patterns of eating, his carbohydrate metabolism and his glucose tolerance.

Relationship between obesity and diabetes

Although many factors contribute to the causation of diabetes, a significant, but still undefined, relationship exists between obesity and the onset of the disease in adults. Institute grantees have been successful in throwing light on this little-explored metabolic territory. They found that nondiabetic obese subjects have, and sustain, significantly higher levels of circulating insulin in response to glucose administration than lean, nondiabetic subjects. These findings suggest that obese subjects are in a "compensating phase" which requires that they secrete an abnormal amount of insulin in order to maintain control of glucose levels. The finding also suggests the possibility that measurement of serum insulin levels after glucose administration may serve as a useful diagnostic tool in detection of the diabetic trait prior to the development of frank carbohydrate intolerance.

Interestingly enough, similar findings were obtained by another group of grantees who derived their results by way of a very different experimental approach. This group has found striking similarities in metabolism between nondiabetic patients with simple obesity and those with maturity-onset diabetes. The NIAMD grantees studied metabolism in response to intra-arterial insulin, in the forearms of young subjects who had recently gained weight and compared the results with normal subjects, and with the known metabolic aberrations of diabetes. The results obtained suggested that in early obesity, insulin, whether already in the body or administered by injection, is less active, metabolically, than in the lean state. As a result, in the obese, larger amounts of insulin are required and are elaborated to facilitate normal carbohydrate utilization. On the basis of these findings, these scientists have postulated an explanation for the relationship between simple obesity and maturity-onset diabetes: Chronic carbohydrate excess in obesity causes an adaptive hyperinsulinism which may lead to eventual exhaustion of the pancreatic islets' ability to maintain the abnormally high insulin output.

Potential new value of oral drugs

NIAMD scientists and grantees are continuing their efforts to identify individuals who are likely to become diabetic long before clinical symptoms appear, with the hope that it may be possible, ultimately, to delay or prevent emergence of frank clinical disease symptoms, through some new therapeutic approach. Institute grantees have demonstrated that prolonged administration of the oral antidiabetic drug tolbutamide results in either a return to normal or improved carbohydrate tolerance in young, nonobese asymptomatic patients with mild diabetes. The beneficial effects of such sustained treatment in this type of patient have now been demonstrated to persist in some patients as long as 4 years. These studies are continuing, and a possibility exists that such drugs may be used as prophylactic or retarding agents against diabetes in patients who are predisposed to this illness.

Treatment of serious eye complication in diabetes

Another outstanding clinical advance worth mentioning deals with a serious complication of diabetes, diabetic retinopathy, recognized as a leading cause of blindness in the United States. Despite previous efforts and interest in pituitary gland surgery as a treatment for diabetic retinopathy, little information has been available on the clinical suitability and rationale of such treatment. NIAMD grantees, encouraged by earlier studies which linked the pituitary gland with certain aspects of carbohydrate metabolism regulation, considered the possibility that a decline in pituitary function would slow or stop the advance of retinopathy, and so performed a unique and highly intricate operation on the pituitary glands of a select group of 13 patients. Postoperative results in 12 patients showed unequivocal, beneficial changes in vision, including clearing of glassy haze and ending of hemorrhagic activity. These encouraging early results warrant further investigation and observation of the effects of this operation on patients with advanced diabetic retinopathy.

NEW DEVELOPMENTS IN SURGICAL RESEARCH

Modern surgery plays an inestimable therapeutic role in many diseases in the area of responsibility of the NIAMD, and the Institute supports a large number of surgical investigators whose methods have stimulated previously stagnant areas.

Use of bone for hip fracture repair

For example, one Institute grantee has successfully introduced the use of specially processed cortical bovine bone as a substitute for metal pins in repairing hip fractures in individuals with osteoporosis. In the past, in skeletal repair, grafts using bone other than that derived from the same individual had a major difficulty: The host tissues would invariably "reject" the foreign, transplanted bone through defensive immune recations. A practical method has been developed at the Squibb Institute for Medical Research of treating bone to remove serum, cells, and fats, the main sources of antigenicity and thus of graft rejection. This method involves prolonged washing of the bone with detergents, removal of fat with special solvents, and rinsing in sterile water for 5 days.

An Institute grantee has been using dense bone from full-grown bulls, processed in such a fashion, in the repair of hip fractures in osteoporosis and has found that this material becomes even better integrated into the final, repaired bone than autografts (transplants from the same individual). The investigator has reported that the hips of 50 osteoporotic patients, each 70 or more years old, are now even "stronger than natural hips," after having been repaired in this fashion.

Osteoporosis, a bone-thining disease characterized by demineralization (primarily loss of calcium), is often found in postmenopausal and aged patients. After a study of the literature of fractures of the hip, this investigator concluded that when metal pins were used to repair hip fractures in osteoporotic patients, the appliance did not immobilize the fragments completely, the adjacent bone crumbled and was resorbed, and the final result was failure of the bone to knit in about 50 percent of cases, compared with failure in about 30 percent of nonosteoporotic patients.

The method or processing the bone graft involves sterile removal of the material from bovine carcasses, chemical extraction of antigenic proteins (but preservation of collagen and bone minerals as far as possible), drying, cold sterilization and packaging in sterile containers. Pegs fashioned from this material are subsequently used to pin together the fractured neck of the patient's hip bone. The results suggest processed cortical bone is well tolerated, and superior to metal in that it is cemented firmly to the surrounding host tissue and incorporated inextricably into the host skeleton. It is resorbed very slowly if at all. Moreover, it frees the patient of the discomfort of casts and prolonged immobilization in bed.

Success in tracheal prosthesis

After more than 10 years of painstaking research, other grantees of this Institute have reported success with permanent prostheses of Teflon in the tracheas of experimental animals. This process will be of invaluable aid in surgery in man for lesions involving the trachea, a difficult problem for plastic repair.

The problems raised by removal or destruction of sections of the tracheobronchial tree (primarily because of traumatic injuries) have long defied solution. Primary anastomosis, a direct union of the remaining parts of the tracheal tube, would be the ideal solution but can be performed only when small segments have been removed, and even then, obstructive narrowing usually occurs at the site of union. Despite 10 years of investigation, attempts have failed to find a method of restoring permanently a well-functioning tracheo-bronchial system after removal of long sections of the tracheal tube.

After studying many different plastic materials and prosthetic devices, the investigators developed a flexible, helically corrugated Teflon tubule fitted with meshlike ends of soft polyethylene. They have uniformly had permanent success with implantation of such a device in the tracheas of a large series of experimental animals. The designers of the prosthesis feel that they are now ready to apply their findings to the clinical use in man.

Surgery of the gastrointestinal tract

During the past year, Institute-supported scientists were responsible for particularly important surgical developments in the area of gastroenterology. Recent experimental studies have indicated that the stomach and intestines can be added to an ever-growing list of organs which can be successfully transplanted within the body (autografting) and which may retain their original function in the new site.

Much can be gained from studies of such experimental autografts: An increase in surgical knowledge from working with innumerable gastric and intestinal surgical translocations and enhanced knowledge of the physiological functioning of organs under altered conditions. Out of such studies may evolve new treatments for conditions such as ulcerative colitis, enteritis, and peptic ulcer, diseases about which we, as yet, still know all too little.

Aid to absorption after intestinal resection

Other grantees have reported an unusual, dramatic method to manage the problem of malabsorption following massive intestinal resection. Extensive resections of the small intestine are most frequently performed for major gangrenous involvement of the intestine following vascular occlusion or volvulus (intestinal "twisting"). When large portions of the small intestine are removed, the immediate mortality may be high and the majority of those who survive develop an often-fatal, short-bowel syndrome with clinical features of malabsorption, such as diarrhea, inability to digest fats, severe weight loss, and anemia.

Earlier investigators showed that long-term survival was possible in the dog when a short reversed segment was interposed in the continuity of the intestinal tract. In this short segment the direction of the intestinal waves of contraction, and thus of the motion of intestinal contents, is reversed. This results in the local introduction of a brief "upstream" mobility into the generalized "downstream" trend, delaying the total transit time of vital food material and promoting increased absorption. The NIAMD grantees successfully carried out the "surgical reversal" method in the case of an 84-year-old patient with continued good results, and demonstrated the feasibility of the method for further trials.

GASTROENTEROLOGY

New therapy for pancreatitis

Another development of NIAMD grantees involves an effective new treatment for pancreatitis, a disease often acutely fatal. The complete pathogenesis of this disorder has never been clearly defined. Premature activation of a protein-digesting enzyme, trypsin, in the pancreas, however, rather than later in the intestine, may be an important cause of this catastrophic illness.

The NIAMD grantees tested a new trypsin inhibitor, isolated from the parotid glands of cattle, in experimental animals. Following successful treatment of experimentally induced pancreatitis in laboratory animals, the investigators successfully treated bouts of recurrent, acute pancreatitis in human patients. Relief of the intractable pain, and of the attacks, without side effects was obtained within 20 minutes. Evaluation of the new agent continues at the present time.

Diagnostic aid for abdominal diseases

In studies designed to improve diagnostic aids of various gastrointestinal diseases, another group of Institute grantees found that determination of ammonia levels in peritoneal fluid may be of distinct value in the differential diagnosis of acute abdominal conditions.

Microbial putrefactive processes in the gastrointestinal tract normally lead to the formation and local accumulation of ammonia. Based on this observation, the investigators have developed a new diagnostic approach involving measurement of the ammonia content of the abdominal fluid after spillage of intestinal contents attendant to acute intraabdominal lesions.

This new diagnostic technique permits differentiation, on the basis of ammonia concentrations in peritoneal fluid, between pancreatitis and hemorrhage due to ectopic pregnancy, ruptured ovarian cyst, or ruptured spleen, on one hand, and perforation of strangulated intestinal loop, appendix, or duodenal ulcer, on the other.

Gallstone origin clarified

NIAMD grantees have found new evidence to clarify the origin of gallstones. Although cholelithiasis (gallstones) is not an uncommon disease, the question of how stone formation actually begins remains unanswered. Based on studies with experimental animals and patients, the NIAMD grantees found that bacterial infections caused primarily by *Klebsiella pneumoniae*, may be responsible for a metabolic derangement in the liver that results in the formation of an abnormal compound, ornithocholanic acid. This compound lowers the solubility of normally present cholesterol and bile pigment in bile, "salts them out of solution," and thus sets the stage for cholesterol and bile pigment to precipitate out of the bile and form the nucleus of a gallstone. This would cause a continuing irritation of the gallbladder and the stone would then grow much as a pearl does in an oyster.

METABOLIC AND MOLECULAR DISEASES

Just about half a century ago the eminent English physician, Archibald Garrod, assembled a group of diseases under the descriptive phrase, "inborn errors of metabolism." He dealt, at that time, with only six diseases which shared common characteristics. Not only has the number of recognized hereditary metabolic errors increased immensely in the past half century, but the understanding of many of these is far more precise and more sophisticated than was ever envisioned by Garrod.

The 11th International Congress of Genetics which met recently heard several reports that the incidence of these inborn errors of metabolism may be appreciably higher than is generally recognized. The increased number of patients with these diseases stems from improved medical management resulting in a greater number of surviving patients, and from improved recognition and diagnosis. Because of these factors, we may be facing a future with more and more patients who have inborn errors of metabolism of varying severity.

New cause of jaundice in infants

At this time I would like to report to the committee on how foresight, close communication and cooperation, and scientific perspicacity established the cause of severe jaundice of previously unknown origin that occurs in some newborn babies, at times leading to permanent brain damage and mental retardation. About 2 years ago an Institute grantee examined a 2-week-old infant with severe jaundice from no apparent cause. He took a sample of the mother's milk and held it for analysis, suspecting that it might contain some jaundice-producing factor.

Later, the grantee communicated with another Institute-supported scientist who had previously discovered a unique steroid substance in the blood of a number of women who had consistently given birth to severely jaundiced infants. Cooperating closely, the two scientists then found the same unusual steroid compound in the specimen of milk the first scientist had originally collected.

Their studies demonstrated that the new substance (3-alpha, 20-beta-pregnanediol) inhibited a vital enzyme reaction which ordinarily transforms bile pigment (bilirubin) into a form excretable in the urine. Samples of milk from additional mothers with jaundiced babies revealed the same inhibiting effect on bile pigment metabolism. All of these babies recovered from their jaundice when breast feeding was interrupted.

The exact mode of action of the new compound is not entirely clear, but it is believed that it acts as a competitive inhibitor of an enzyme needed in the chemical chain of events leading to the normal urinary excretion of bilirubin. When bilirubin accumulates in the body, it leads, progressively, to clinical jaundice and tissue damage. In its severest form, this process is associated with degenerative changes in the central nervous system and eventual mental retardation. The NIAMD grantees are now studying the mechanism responsible for elaboration of the unusual steroid compound.

Growth hormone test provides practical source

In an effort which promises almost immediate clinical applicability, NIAMD grantees evolved a valuable diagnostic test for acromegaly (selective gigantism), as well as a possible source for human growth hormone, a substance needed for the treatment of pituitary dwarfism. The only source now available is human pituitary glands obtained at autopsy, since growth hormone derived from other animal species, such as the cow, has proven to be inactive in man. These scientists have developed a method of extracting biologically active growth hormone from human urine and measuring it with new, delicate immunologic technics. Using these methods, which are more sensitive and more feasible than the conventional assay of human growth hormones in plasma, the investigators discovered a potential source of growth hormone in acromegalic subjects whose urine contains 10 times the amount of the hormone found in normal urine. The large amounts of growth hormone detected by this new method in the urine of patients with acromegaly offers a valuable diagnostic test for this condition and may provide a long-sought-for, practical source of the hormone needed for the treatment of pituitary dwarfism.

Cystic fibrosis

Cystic fibrosis ,a metabolic disease formerly considered limited to children, is being found increasingly in the adult population. The committee is well aware, from previous testimony, of the characteristics of this hereditary disease of children and adolescents, involving a generalized malfunctioning of the mucus, sweat, and related exocrine glands. It is often a fatal disease in which chronic and progressive pulmonary disease is the most critical development. Over the past 2 years, studies have shown that there are far more adults than previously believed, who carry a partial genetic endowment for the disease but who do not display the full gamut of clinical symptoms characteristic of the disorder.

The principal aim of investigations in the Institute's Pediatric Metabolism Branch is to uncover and elucidate the basic defect in mucopolysaccharide metabolism presumably responsible for the abnormal secretory activity accounting for the clinical manifestations of the disease. In order to open up new avenues of research on cystic fibrosis, this past year the Branch has initiated a combined immunological and biochemical approach.

This approach is based on the assumption that the defective, viscous mucus of cystic fibrosis contains an abnormal mucoprotein component which can give rise to the production of antibodies when injected into animals. Once having obtained the immune sera from suitable animals, it may be possible, utilizing a variety of immunologic and biochemical methods, to isolate the mucoprotein which is specifically abnormal, in children with cystic fibrosis, and possibly in their parents, and in other asymptomatic carriers which represent from 2 to 5 percent of the general population.

Fundamental research, the genetic code

In my last report to you, I covered in depth our studies on the genetic "code of life," its implications for research attacks on the inherited diseases, and its mechanism by which hereditary information is perpetuated from generation to generation, enabling living matter to reproduce itself systematically. Our investigators, both intramurally and extramurally, are continuing their studies of the two nucleic acids DNA and RNA (deoxyribonucleic acid and ribonucleic acid) which contain the basic genetic secrets governing heredity, and hence, all of life on earth.

I have already mentioned to you the first successful synthesis of insulin by NIAMD-supported basic scientists. In work of great significance in medical genetics, other workers supported in part by NIAMD have reported the first partial synthesis of ribonuclease, an enzyme which breaks down RNA. They have also found that the synthesized peptide containing the first 13 amino acids of the ribonuclease chain-like molecule demonstrates 70 percent of the catalytic activity found in the natural enzyme. This finding supplies long-sought information on the enzyme's "active site," that part of its molecule which holds the key to its function. Synthesis of this vital enzyme in genetic biochemistry is another important step forward toward the time when the key substances in control of genetic life processes might be amenable to some measure of manipulation and control.

Award-winning grantee

I am happy to report that one of our grantees, Dr. Lyman C. Craig, has been named a winner of one of the 1963 Albert Lasker medical research awards. Dr. Craig received the award for his creation and continued development of the now widely used countercurrent distribution technique and apparatus, as an effective method for the separation of biologically and clinically significant compounds. This method has proven crucial in the establishment of the structure of insulin and is indispensable in the extraction, isolation and purification of specific compounds from impure, complex, biological materials.

SCIENTIFIC COMMUNICATIONS

As a direct result of the great expansion of biomedical research which has taken place during the last decade, a tremendous amount of scientific information is being turned up which must be made available to research workers in pertinent fields for fertilization of their investigational efforts, and must be conveyed to the community of practicing physicians in order to bring the benefits of this research to the bedside of the patient at the earliest possible moment. I told you last year that we are conscious of the magnitude of the "communication problem," which involves an increasing amount of new unfolding knowledge on one hand and larger than ever audiences to which this knowledge must be conveyed to be of value, on the other.

The Institute is engaged in vigorous, and I believe successful, efforts to expedite this process of communication of scientific findings. We are carrying out a major program of communications which includes strong selective support of primary and secondary scientific publications, translation of pertinent research findings published abroad, and the stimulation, promotion, and support of personal interchange between scientists through working conferences and symposia. The latest advances in specific diseases are being brought to the attention of tens of thousands of practicing physicians through the Institute's very active program of comprehensive scientific exhibits and informative and useful literature which accompanies them. At present we are in the midst of planning the production of clinical motion pictures for information and postgraduate education purposes. In the field of arthritis and rheumatic disease, there will be forthcoming a periodic bibliography of the relevant literature (based on the new automated medical literature retrieval system of the National Library of Medicine), and the initiation of a much-needed monthly abstract service which will convey to American research workers condensed, up-to-date scientific research findings gleaned as fast as they appear from the scientific literature from all over the world.

I am also proud to report that the comprehensive electronic storage and retrieval system for information on diabetes, which this Institute is supporting at the University of Minnesota and which I mentioned to you last year, has disseminated its first valuable and concrete product, a bibliography of over 2,500 recent diabetes-related articles, to interested American research workers and practitioners in the diabetes field.

It has been my observation that this Institute operates effectively, intramurally as well as extramurally. The Institute's intramural and grants-in-aid programs have resulted in a wealth of new scientific knowledge, some of it of immediate applicability at the bedside, and some of it indispensable as a basis to continued productivity in biomedical research. My statement here today describing findings by our scientists and grantees has just touched upon a few of these results. The sum total of these efforts is found in untold presentations in the contemporary scientific literature and was reported to the community of medical practitioners and biomedical research scientists in numerous working meetings and conferences. The width and depth of these efforts are such that it is still impossible at this point to gage the full extent of progress against disease which they have engendered and will engender in the future.

THE SIGNIFICANCE OF TRAINING

Thus far, I have not mentioned another important responsibility, assigned by Congress to this Institute—that of support of research training of young biomedical scientists in its area of purview. I firmly believe that our country's most vital resources lie not in what is buried in the soil but in creativity in the brains of its people, finely honed by pertinent training. The world does not abound with a surfeit of Columbuses and Einsteins, and we must give the scientists we have the skills and training which will enable them to shape a highly productive future. In brief, an adequate pool of highly trained skilled and imaginative scientific manpower is the key to conducting meaningful research and obtaining worthwhile results. Compared with the urgent needs of the present and particularly of the future, the supply of this elusive commodity is becoming meager. Future advances in biomedical research depend on continued development of a highly trained force of scientists. Adequate support by this Institute in the form of training grants and fellowships is essential to forestall a harmful interruption of the on-going vital training process and to prevent costly future setbacks to the overall improvement of health.

Mr. Chairman, I am submitting a request for $113,176,000 as compared with the operating level of $106,225,000 for 1964. The proposed increase for 1965 will provide for an estimated 130 additional research projects in arthritis, diabetes, gastroenterology and various metabolic diseases. This request for 1965 is distributed among program activities as follows:

Grants:	
Research	$80,261,000
Fellowships	3,979,000
Training	13,690,000
Subtotal, grants	97,930,000
Direct operations:	
Research	11,867,000
Collaborative studies	1,597,000
Review and approval	1,491,000
Program direction	291,000
Subtotal, direct operations	15,246,000
Total 1965 appropriation request	113,176,000

Dr. Whedon. Mr. Chairman and members of the committee, the 1965 budget request for arthritis and metabolic diseases is for $113,176,000 as compared with $106,225,000 available for the current fiscal year. The increase will provide for expansion and intensification of research activities in our fight against arthritis, diabetes, osteoporosis, cystic fibrosis, and many other disabling disorders. It will support clinical as well as basic research and research on prevention as well as cure, on identification and diagnosis as well as treatment.

The past year has been a fruitful one, with accomplishments ranging from the synthesis of insulin to improvements in the treatment of rheumatoid arthritis. Significant gains have been made in diagnosis and treatment procedures for diabetes, gout, and diseases of the gastrointestinal tract. A new and different cause of infantile jaundice has been discovered, enabling prevention, in the future, of possible resultant mental retardation in many children. New surgical procedures have been developed, improving treatment for patients suffering from such disorders as hip fractures in osteoporosis and lesions of the respiratory and gastrointestinal tracts.

The proposed increase for 1965 will provide for an estimated 130 new research projects in arthritis, gastroenterology, diabetes, and other metabolic disorders. Of the total budget, $97,930,000 will be allocated for grants, and $15,246,000 for direct research and supporting services.

Mr. Fogarty. Will you highlight some of the answers that you just referred to in various categories?

Dr. Whedon. I will be glad to. If I may, I would like to set the tone of my testimony and say that, in the summary that I have just read, I would hope that you would view that summary, and also what I am going to present not just as a single year's accomplishment, but in a context of an ever-flowing river of progress with substantial success against disease year after year.

Some of the diseases are stubborn and for the moment seem unyielding. But in the main, there has been a succession of instances of meaningful increases in our understanding of biomedical problems and of practical contributions to therapy, as a result of the programs supported by our Institute, funded by the Congress, as recommended by your committee.

Now with regard to specifics, I think probably the outstanding accomplishment of this year has been the synthesis in the laboratory of a biologically active artificial insulin molecule.

Now, the activity of this artificial insulin molecule is not as great thus far as that of the natural insulin derived from animal sources, but nevertheless this preparation will be an invaluable research tool for studying the mechanism of natural insulin in diabetes. In addition, this synthesis is an important step toward eventual production of synthetic insulin for possible therapeutic use by injection in certain cases of diabetes.

Mr. DENTON. I did not quite understand what you discovered.

Dr. WHEDON. In the laboratory, Mr. Denton, chemists have been able to put together an artificial insulin molecule. What they have done has really been an outstanding achievement of organic chemical synthesis. We have known for some time what the structure of insulin was, that it was made up of 51 amino acids—you know, the building blocks of protein—and that these 51 amino acids were arranged in two different chains called the A chain and B chain. So, what the chemists had to do was to put together 20 amino acids for the A chain and then put together 31 in the B chain, and then hook up these two chains in just the right way in order to bring about the physiological action of the insulin molecule.

They found that their synthetic molecule was not as active as the natural insulin, which we get from the pancreas glands, you know, of animals. In trying to determine why, they hooked up a synthetic A chain with a naturally derived B chain and found out that it had the full activity of insulin. So, they suspect that more work needs to be done on the synthesis of the B chain in the laboratory. Possibly impurities are inhibiting some of the action of the key amino acids in this linkage of 31 amino acids.

Now, as I say, we are predominantly interested at the moment in the usefulness of this synthetic insulin as a research tool for learning more about the way in which insulin brings about its various actions in the body, the most well known, of course, being the reduction of the level of sugar in blood.

The chemists can now synthesize various fragments or various analogs—that is, other insulins made up of slightly different amino acid composition—and this will enable them to determine just exactly which combinations of amino acids or what parts of the molecule are responsible for the action of insulin.

The other important thing is, when you can completely synthesize a very complicated chemical substance of this nature, you can fit in at almost any point you want a radioactive tag. You can put in a tagged carbon or tagged nitrogen or tagged hydrogen, for example, and this will enable you to follow the course of this substance through the body and find out the ways in which it is inactivated or destroyed, or find out the places in the body to which it will go and thereby exert its effect.

But in addition to this basic information that we will get out of this achievement, there is the possibilty that we shall arrive at a synthetic insulin that will be useful in the treatment of certain patients who have a resistance to the natural insulin which we obtain from the pancreas, primarily of sheep, but also sometimes from hogs.

In some of these patients, the injection of insulin acts as an antigen. It produces an undesirable, defensive, immune response which may severely reduce the therapeutic effectiveness of the insulin, so that rather large quantities of insulin may need to be given in these patients to have any effect on controlling the blood sugar.

Thus, if we could synthesize a pure nonantigenic insulin molecule or make related analogs which are therapeutically effective, we can get around this resistance to insulin that occurs in a few patients.

Mr. Chairman, I have two comments: One, this is an example, I think, of the type of activity where it is useful to have more than one laboratory, more than one university or medical center working on the same problem. The question of duplication of effort has arisen, particularly in recent years, and I hope it is clear that when you have as difficult a chemical job to do as putting together 51 different units in just the right combination so that they will act, that it is most important to have more than just one individual or even one group working on this problem. This is true with regard to the synthesis of adrenocorticotropen (ACTH), which we described some 2 years ago, and it is quite true again in the case of the insulin molecule.

SPECIAL REPORT ON DIABETES

The other thing I wanted to say was simply that we have a special report on diabetes prepared for the committee which we will be happy to submit.

Mr. Fogarty. We shall put that in the record.

(The information referred to follows:)

Special Report—Diabetes

INTRODUCTION

During the past few years, diabetes research has witnessed a significant advance in, and application of, knowledge toward improving the well-being and life expectancy of diabetic patients. This has occurred principally through new methods for earlier diagnosis; improved means of control, including particularly the oral antidiabetic drugs; and deepening knowledge of the disease itself. These advances are especially significant in the light of recent statistics released by the American Diabetes Association, which forcefully bring to mind the widespread occurrence of this disease and its much underestimated impact on our population. It is now estimated that there are approximately 3 million diabetic patients in our country. Moreover, from genetic knowledge of the disease, about 5,125,000 other persons living today in the United States are potential diabetics, who will develop the disease some time during their lives.

A complex disorder, for which there is no known permanent cure, diabetes is the seventh ranking killer in the list of diseases that cause death. It affects individuals predisposed to the disorder by their hereditary background. The obvious defect in diabetes is the body's inability to metabolize carbohydrates normally. As a result, the diabetic is unable to utilize efficiently all of the carbohydrates he consumes and to turn them either into heat and energy needed for normal body functioning or to store them in the form of glycogen. Instead, the carbohydrates, converted into glucose, accumulate in the blood and spill over into the urine. Primarily, this occurs because of a diminished supply or availability of active insulin, a hormone produced by the pancreas, although many other factors are now known to be involved. There may be impairment in the action of available insulin and there are concurrent disturbances in the metabolism of fats and proteins, as well as of carbohydrates.

Although the disease can be fatal, properly treated in most cases it can be well controlled. Most diabetics today, with proper treatment, can lead a normal life and live almost as long as their fellow human beings. In a minority of cases, however, although the abnormal blood sugar level can be held in check, the long-term complications of diabetes, primarily those affecting the blood vessels, peripheral nerves and the eyes, are as yet difficult to control.

The generally encouraging outlook is being substantiated by studies conducted at the National Institute of Arthritis and Metabolic Diseases (NIAMD), as well as Institute-supported studies at universities and non-Federal research centers. During the past year, NIAMD-supported investigators have added much to the body of knowledge concerning this complicated disease. In addition to succeeding, for the first time, in synthesizing small quantities of insulin in the laboratory, they have found a method which may be useful in arresting the progress of mild diabetes in young patients, developed a new method of detecting early diabetes, and uncovered additional evidence pointing to obesity as a forerunner of the disease.

SYNTHESIS OF INSULIN

Ever since the discovery of insulin in 1921, progress in the effort to synthesize an active product in the chemistry laboratory has been extremely difficult. Just a few months ago, however, NIAMD grantees at the University of Pittsburgh culminated 5 years of research in this direction by synthesizing the two major components of the insulin molecule, composed of an A and a B chain of amino acids in specific order.

Slight, but definite, insulin activity was generated by combining the two chains. Although the activity of the molecule resulting from this combination is at present far less than that of insulin isolated from animal sources, this, as yet crude, preparation may be a valuable research tool for studying the mechanism of insulin action in diabetes. Moreover, this synthesis is an important step toward eventual production of synthetic insulin which possibly will have therapeutic use in patients allergic or resistant to the natural product.

Treatment of all cases of juvenile diabetes and of severe adult diabetes would be impossible without the daily administration of insulin, which is presently obtained by isolation and purification from the pancreas of various animals. In some diabetic patients this product, depending on the animal species from which it is derived, acts as an antigen, producing a specific undesirable "defensive," immune response which may severely reduce its therapeutic effectiveness. The present work opens the way to the synthesis of an insulin identical to that normally produced by man or of releated analogs which may be therapeutically effective and which may be less prone to induce resistance in patients. Synthesis of the complex molecular structure of insulin entailed a highly sophisticated chemical process involving the correct alinement and linkage of 51 amino acids in two separate chains and proper coupling of the chains. The work is a triumph of fundamental laboratory research.

OTHER INSULIN STUDIES

Isolation of insulinlike "exercise factor"

The ability of exercise to promote metabolism of sugar in the absence of naturally present or administered insulin is well known. This insulinlike effect of strenuous exercise was first reported by an Institute grantee to be the result of release of a specific factor from working muscle into body fluids. Subsequent attempts to isolate and identify the factor were frustrated until recently when this same grantee reported that by including strenuous muscular exercise in diabetic dogs and collecting blood and lymph from the animals, he was able to isolate a humoral, hypoglycemia-inducing factor. Though similar to insulin in metabolic actvity, the factor appeared to be chemically and immunologically distinct and did not originate in the pancreas, as does insulin. It is, the investigator concluded, a separate and unique product, probably released from muscle.

Action of insulin

The ways in which insulin affects carbohydrate metabolism are still not fully understood, but studies are continuing in this area of basic research.

One NIAMD scientist has recently completed a study of the effect of insulin on glucose release from the liver. An early hypothesis held that abnormal releases of glucose by the liver was one of the causes of high blood sugar levels and of spillage of glucose into the urine. Insulin, it was assumed, inhibited the release of glucose by the liver, but evidence for this effect was not fully convincing because suitable research techniques were not available.

Through a sensitive laboratory method, the NIAMD scientist has found now that insulin consistently inhibits glucose release from extracts of liver from experimental animals. His results suggest that one of the principal actions of insulin in the liver is suppression of conversion of protein to glucose.

NEW PATHOLOGIC ASPECTS

Evidence of the variety of altered metabolism in diabetes, hitherto unknown, was reported recently by grantees who discovered abnormal interior bone remodeling behavior, associated with a decrease in new bone formation, in adult diabetics. The finding of this previously unsuspected bone abnormality suggests that further study of disturbed bone physiology in diabetes may provide some insight into the altered cellular metabolism in this disease.

NEW DIAGNOSTIC AIDS

Diagnosis of diabetes is aided by the standard glucose tolerance test, and by the more sensitive cortisone-glucose tolerance test, both of which are designed to measure glucose utilization by the body. New and better methods of detecting the disease are appearing, however, as the result of current research. During the last 12 months, Institute grantees succeeded in developing a new diabetes screening test which involves the use of one of the oral antidiabetic drugs, tolbutamide, which is believed to stimulate the pancreas to release insulin. Their oral tolbutamide-glucose tolerance test distinguishes the diabetic from the normal subject by the manner in which insulin is released from the pancreas following stimulation with the drug; in the diabetic there appears to be a sluggish or inadequate release of insulin following tolbutamide administration. The resulting delayed response of the lowering of blood sugar levels permits separation of the diabetic from the normal subject. This test is simple, apparently accurate, and has minimal side effects. warranting its inclusion among the diagnostic aids now used to detect diabetes.

A finding by another group of grantees, meanwhile, has provided evidence that the periodicity or spacing of food consumption can affect carbohydrate metabolism and subsequent standard glucose tolerance tests to detect diabetes. This was demonstrated by investigators who showed that "nibblers" who eat small but frequently spaced meals display a definite increase in tolerance to carbohydrate, as determined by the tests, while "gorgers" who eat only two large meals each day may appear to be diabetic by the same criteria. In other words, whether an individual nibbles his food over a period of time or gorges himself on the same amount of food at one sitting during the days preceding the test, dramatically affects his carbohydrate metabolism, and consequently, the results of subsequent tests to detect diabetes.

Thus, proper dietary management for the standard glucose tolerance test should take into account not only the quality and quantity but also the periodicity of the food ingested on preceding days.

RELATIONSHIP BETWEEN OBESITY AND DIABETES

Weight control is important in the management of diabetes, as evidenced by the fact that 6 of 7 diabetics over the age of 40 have been found to be overweight before onset of the disease. Although many factors are undoubtedly involved in the causation of diabetes, a significant, but still undefined relationship exists between obesity and the onset of the disease in adults. NIAMD grantees exploring this relationship reported last year that nondiabetic obese individuals were found to have significantly higher, sustained levels of circulating insulin in response to glucose administration than did lean, nondiabetic subjects.

These findings suggest that obese individuals are in a "compensating phase" which requires that they elaborate an abnormally large amount of insulin in order to maintain control of glucose levels. This raises the possibility that measurement of serum insulin levels after glucose administration may serve as a useful diagnostic tool in detecting the diabetic trait prior to the development of frank carbohydrate intolerance.

Interestingly, similar findings were obtained by another group of grantees who derived their results by way of a highly divergent experimental approach. This group found striking similarities in metabolism when they compared nondiabetic obese individuals with maturity-onset diabetes patients. The grantees studied metabolism under normal conditions and in response to intra-arterial insulin in the forearms of young subjects who had recently gained weight, and compared the results with those obtained in normal control subjects, and with the known metabolic aberrations of diabetes.

Results suggested that in early obesity a state of hyperinsulinism may exist coupled with resistance to both body insulin and administered insulin. On the basis of these findings, the investigators postulated that chronic carbohydrate excess in obesity causes an adaptive hyperinsulinism which ultimately may lead to exhaustion of the ability of the pancreas to maintain its abnormally high insulin output. This could, of course, lead to hypoinsulinism and diabetes, thereby providing another link in the chain of evidence incriminating obesity as a possible precursor of maturity-onset diabetes.

POTENTIAL NEW VALUE OF ORAL ANTIDIABETIC DRUGS

Since 1957 three chemicals have been made available which can be taken orally and which have the remarkable effect, for many maturity-onset diabetes patients, of reducing their blood sugar to safe levels without the injections of insulin they heretofore had to take. Two of these drugs, tolbutamide and chlorpropamide, come from the same chemical family, the sulfonylureas, to which the famous antibiotic sulfa drugs belong. The third and newest of the oral medicines is phenformin.

In line with their continuing efforts to identify individuals who are likely to become diabetic long before clinical symptoms appear and to provide effective treatment, Institute grantees last fall reported successful use of tolbutamide in arresting mild diabetes in young, nonobese asymptomatic patients. They demonstrated that prolonged administration of this oral antidiabetic drug resulted in either a return to normal, or improved, carbohydrate tolerance in such patients. The beneficial effects of such sustained treatment have thus far been shown to persist in some patients as long as 4 years.

It is significant that tolbutamide, used heretofore primarily in the treatment of maturity-onset diabetes, appears to be effective in arresting early, mild diabetes in young, nonobese individuals. The possibility has been suggested that such drugs be used as prophylactic or retarding agents against diabetes in patients who are predisposed to this disease.

COMPLICATIONS OF DIABETES

Neglect of diabetes may lead to development of complications such as heart disease, failing eyesight, and hardening of the arteries. Although concentration primarily on the cause and prevention of the basic disease, researchers today are also vitally interested in these complications in the older diabetic, inasmuch as his life expectancy and function depend on them to a large extent.

Many persons whose diabetes begin in childhood and who have had it 20 years or more develop failing eyesight due to progressive damage to the retina. Last fall Institute grantees reported encouraging results in retarding diabetic retinopathy, a leading cause of blindness, by pituitary gland surgery in a selected group of patients. Encouraged by earlier studies which linked the pituitary gland with certain aspects of carbohydrate metabolism regulation, they considered the possibility that a decline in pituitary function would slow or stop the advance of this complication of diabetes. Postoperative results in 12 of 13 patients, following the unique and highly sophisticated operation, showed unequivocal, beneficial changes in vision, including clearing of glassy haze and ending of hemorrhagic activity. Prior to this study, little information had been available on the basic phenomenology and clinical suitability of this therapeutic procedure. These encouraging early results warrant further investigation and observation of the effects of this operation on patients with advanced diabetic retinopathy.

IMPROVED COMMUNICATIONS OF RESEARCH DEVELOPMENTS

One of the important tasks facing any scientific investigator today, including those in the field of diabetes, is that of keeping abreast of current research developments. Considering the breadth and depth of ongoing diabetes-related studies, maintaining meaningful current awareness is becoming increasingly difficult. The Institute is acutely aware of the need for adequate current awareness and improved scientific communicatitons. Consequently, in recent years, the NIAMD has extended major financial support to the establishment of a comprehensive diabetes abstract-translation-microcard-retrieval program. This system combines facilities for collecting all diabetes data published, and coding this information into an electronic storage and retrieval network. This information system will be very useful in supporting future research efforts. The first stage in this effort, which involves activities at three different universities, reached fruition this last year with the publication of a bibliography of more than 2,500 recent diabetes-related articles which had been selected from the cumulative Index Medicus of the National Library of Medicine. This valuable bibliography was prepared in the form of a printout from a computer into which, originally, diabetes literature citations had been fed for storage.

Subsequent bibliographies being prepared will bring this service up to date. In addition, a new current-awareness bulletin covering all recent literature in diabetes and related subjects is planned for distribution to interested investigators and practitioners, in the future. Contents of this bulletin would be based on information which is constantly being entered into storage in computers. These various new communication techniques will provide an up-to-date alerting service to help keep diabetes investigators aware of current developments in their field.

OUTLOOK

Between the time that insulin was discovered in 1921 and its molecular structure was determined in the midfifties, some 35 years elapsed. By contrast, NIAMD grantees were able to synthesize the insulin molecule and generate insulin activity in the laboratory within the relatively short space of 5 years. Such a significant development in such a short period of time serves to point up the phenomenal progress which has been made in the fight against diabetes in recent years. Although there is still no permanent cure for the disease, new and improved methods of detecting and treating the diabetic are constantly being adopted, and even treatment of the asymptomatic prediabetic has been suggested. Now that this once uncontrollable disease can be controlled, we hope that deferment of its onset in predisposed individuals, suppression of its severe complications and its eventual prevention are not beyond the realm of possibility.

INCREASED KNOWLEDGE OF RHEUMATOID ARTHRITIS

Dr. WHEDON. Now, another instance of accomplishment which I think will be of considerable interest to the committee is the fact that we have learned during the past year considerably about various factors which bring about and influence the development of rheumatoid arthritis. This increase in knowledge has been brought about by epidemiological studies—that is, field studies—which have been known as a tool which may clarify the respective roles played by environment and heredity.

Last year you may remember that I mentioned the first stage of this study in which the group from our own Institute in Bethesda went out among the Blackfeet Indians in Montana and examined a large number of them and took blood samples from these individuals to see what the incidence of the so-called rheumatoid factor was, not only in patients with rheumatoid arthritis among the Indians, but among their relatives and many others in the tribe.

Now I can report to you the completion of this study, which is part of a program designed to ascertain if populations living under different geographic and climatic conditions differ in frequency or type of arthritis. The populations, as I mentioned, included the Blackfeet of Montana, who inhabit one of the coldest areas in our country, and the Pima Indians of Arizona, who live in one of the warmest areas of the country. These Indian tribes have lived virtually their entire lives in their respective reservations, which are located in their ancestral homes, and hence should reflect environmental influence on the occurrence of disease to a far greater extent than most other population groups. Also these tribes were picked because they are relatively isolated, so that the familial or blood relationships could be detected and much more accurately evaluated than has been the case in other population studies along this line.

The investigators were able to examine more than 2,200 Indians, representing approximately 85 percent of all of the Indians in these two tribes over 29 years of age. What they found was that the occurrence of rheumatoid arthritis was not tied to hereditary factors. In other words, the rheumatoid factor which can be analyzed in the blood was not more frequent in the relatives of patients than in nonpatients. This is a finding different from what had been noted previously and which we have reported in our earlier testimony to you.

Now, in addition, they found that climate appeared not to be a significant factor, at least not in the sense we had thought of climate affecting rheumatoid arthritis in the past. The prevalence of rheumatoid arthritis was much greater among the Pima Indians living in the warm climates than it was among the Blackfeet Indians living in the cold or relatively cold climate of Montana. Thus, we have made it rather clear that neither climate nor heredity appears to play a significant role in the development of rheumatold arthritis, and this means we must look for other factors as influencing significantly the prevalence of this disease.

TREATMENT OF RHEUMATOID ARTHRITIS

Mr. Fogarty. Are you still using ACTH or cortisone for treatment of rheumatoid arthritis?

Dr. Whedon. ACTH is rather rarely used in the treatment of rheumatoid arthritis, but cortisone and related corticosteroid drugs still definitely have a role.

Mr. Fogarty. Are they effective?

Dr. Whedon. Yes, they are effective. The general plan of treatment of the patient with rheumatoid arthritis is usually, first, to try what might be termed milder forms of treatment, particularly aspirin and related salicylate drugs and physical therapy.

Mr. Fogarty. Many doctors say, "Take a few aspirins, that is about as good as anything." I have heard that remark quite often.

Dr. Whedon. It certainly is for many patients, particularly if physical therapy is judiciously included, if it is necessary in the treatment of rheumatoid arthritis.

Then, if patients do not respond to this conservative therapy, the physician who is very knowledgeable in this specialty is apt to progress to giving treatment by a means of gold salts. These are usually tried over a period of several months. If they are not effective, then the physician may go on to the administration of corticosteroids. Corticosteroids are quite effective in a very large proportion of patients, but, as I am sure you are well aware, there are certain side effects that can be rater deleterious. So it is important to hold the dosage of this drug down to very manageable and safe levels.

OSTEOARTHRITIS

Mr. FOGARTY. What about osteoarthritis?

Dr. WHEDON. Osteoarthrtis? Yes; this is actually a more prevalent form of arthrtis which occurs more commonly among older people and involves principally the peripheral joints—that is, the outer joints of the extremities—but also may involve the spine or the hip, and can become quite painful.

Mr. FOGARTY. It is quite progressive, is it not?

Dr. WHEDON. This is usually rather gradually progressive and, as I say, is more apt to become serious only later in life.

TREATMENT OF RHEUMATOID ARTHRITIS

While we are talking about rheumatoid arthritis, I might bring out some interesting points with regard to its therapy, since you seem quite interested.

Mr. FOGARTY. Well, there are an awful lot of people in this country who are bothered with arthritis.

Dr. WHEDON. We have made real progress,. I think, through the grantees supported by our Institute, in the treatment of rheumatoid arthritis. I think one of the particularly interesting developments is that we now understand the mechanism of action of gold salts in controlling the disorder. Gold salts have maintained a position of high priority on the list of effective therapeutic agents in this disease over the past 35 years, but how they worked was a mystery until this year. Now it has been demonstrated by grantees of this Institute that gold salts enter the large phagocytic white blood cells, called macrophages, and inhibit the action of a family of enzymes responsible for inflammatory reactions. Moreover, gold salts have been shown to inhibit the production of certain antibodies. In other words, they act in two different ways; gold salts interfere with the painful inflammatory process of rheumatoid arthritis on the one hand, and on the other appear to inhibit the production of antibodies to whatever the antigenic substance is which is provocative of the disease.

Another important development along these lines is that we now have a better way of controlling the toxic effects of gold salts when these undesirable toxic symptoms occur in certain patients if the gold has been given over a very long period of time.

Recent studies have led to the finding that penicillamine—which is not directly related to penicillin—a heavy-metal-binding compound, will sequester gold salts deposited in tissues and enhance the urinary excretion of the metal from the body. In other words, this substance, penicillamine, is what we call a chelating agent that literally puts out its claws and latches onto the gold salt substances in the tissues and pulls them out and carries them away to be excreted.

Thus, we have now a means of giving gold safely over a relatively long period of time, and if toxic reactions do occur, we can take care of these toxic reactions.

EFFECTS FROM ADMINISTRATION OF CORTISONE AND RELATED CORTICOSTEROIDS

Now, you were interested, Mr. Chairman, a moment ago in the action of cortisone and related corticosteroids. I mentioned there were certain side effects from the administration of these drugs so that the dosage has to be carefully controlled.

One of the scientists supported by us has found that if large doses of corticosteroid drugs are administered only once every 48 hours instead of in the conventional way that we have had of giving them about every 6 hours around the clock, there will result less serious side effects. This new mode of administration apparently reduces the undesirable suppression of the natural hormones of the adrenal gland, suppresses the incidence of peptic ulcer, of psychotic reactions, and of infections which, in many cases, accompany the use of corticosteroid drugs if they have to be given in large doses over a long period of time.

One other development under the general subject of progress of treatment of rheumatoid arthritis; we have a coordinated clinic study going on in 11 different universities in the country, and one of the efforts of this multiclinic study is to determine the efficacy of the antimalarial drugs, chloroquin and hydroxychloroquin, in the treatment of arthritis and also in the treatment of systemic lupus erythematosus.

Mr. FOGARTY. What is that disease? I have heard about it.

Dr. WHEDON. If I may just insert a sentence.

Mr. FOGARTY. All right.

Dr. WHEDON. This study has confirmed the usefulness of these antimalarial drugs in the treatment of rheumatoid arthritis.

LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a so-called collagen disease and it is actually difficult to define it more specifically than that. We simply know that it is an obscure, very poorly understood disorder which affects the soft tissues throughout the body, principally muscle.

Mr. FOGARTY. Is it fatal?

Dr. WHEDON. It is frequently progressive and fatal.

Mr. FOGARTY. I heard some person was given 3 to 5 years to live.

Dr. WHEDON. Well, this is not an extraordinary thing to hear with regard to this disease. There may be periods in which the disease will undergo some remission and be less severe for a period of time. But by and large, the course has been ultimate progression to death.

ESTIMATED UNOBLIGATED BALANCE

Mr. FOGARTY. Now, you have $106,225,000 available for 1964 and the request for 1965 is $113,176,000, or an increase of $6,951,000.

Your estimated unobligated balance is relatively small but would you tell us why you estimate almost $1.5 million will not be needed? Is this your estimate or did someone else arrive at this figure?

Dr. WHEDON. This estimate of unprogramed funds was made relatively early and we have the understanding that they can be released later on if we need them.

Actually there was a difference in the method of calculating what our requirements would be in noncompeting, continuation grants, and under the formula used, this was the calculation.

Mr. FOGARTY. What do you think, are you going to use it? What is your best judgment?

Dr. WHEDON. Actually, in the calculation that we made within our own Institute earlier in the year we thought that we would use all of our research grant funds.

We will be able to tell, of course, more specifically after the March council meeting action. If you ask me to make a guess at this time, I think there is a fair possibility that we will be requesting release of the reserve, but I would like to reserve judgment until after the March council meeting.

RESEARCH GRANTS

Mr. Fogarty. As in the other institutes, most of your increase is in research grants, but I notice it is just to level off this part of the program. All of the increase in the regular program is for increased overhead allowances and the cost of continuing projects already started. There is no increase in the number of new projects which you will be able to support, is there?

Dr. Whedon. Mr. Chairman, I believe you are looking at page 12——

Mr. Fogarty. There is no increase in the number of new projects you will be able to support, is there?

Dr. Whedon. Mr. Chairman, the number of new grants for this year is precisely the same as the number last year.

PROGRESS IN AREAS OF GASTROENTEROLOGY AND GOUT

Mr. Fogarty. Now, will you supply for the record a statement on your research activities and what progress has been made in the area of gastroenterology and on gout?

(The information requested follows:)

SPECIAL REPORT ON GOUT

New drugs and a new understanding of the mechanism of action of an ancient drug used in the treatment of gout now afford an encouraging outlook for the victims of this exceedingly painful disorder. In fact, gout can be the best controlled of all the arthritic diseases at the present time.

Gout is a fairly common metabolic disorder whose victims in the United States alone number almost half a million. This figure is more than doubled when it includes the high incidence of asymptomatic relatives of patients with diagnosed cases of clinical gout. These individuals suffer none of the symptoms of the disease, yet diagnostic tests have confirmed the presence of a metabolic defect, characteristic of gout, in their system. Whereas almost 95 percent of the cases of clinical gout are found among males, the incidence of asymptomatic cases is almost evenly distributed between both sexes.

Once considered a result of overindulgence in food and drink, gout is now known to be caused by an inherited defect in body chemistry. This defect, a disturbance in uric acid metabolism, leads to excessively high blood levels of uric acid and accumulations of its salts in various tissues, particularly the joints, where they may cause recurrent attacks of painful acute inflammation. The initial site of excess urate deposits is usually at the base of the large toe; other sites commonly involved include joints of the upper and lower limbs. In advanced cases which have received inadequate treatment, large deposits of urate accumulate in joints and erode the bony structures, leading to severe and often permanent crippling.

TREATMENT

Present treatment of gout recognizes the efficacy of both old and new drugs and is directed through a two-way approach: control of excess urate and relief and prevention of recurring acute attacks of painful arthritis. The advent of relatively new and potent uricosuric drugs (such as probenecid and sulfinpyrazone), which effectively augment the excretion of uric acid in the urine, now makes it possible to lower the level of uric acid in body tissues to normal, thus preventing a buildup of harmful urate deposits. To abort promptly an attack of acute gouty arthritis, the age-old drug colchicine has been prescribed since it was first extracted from the meadow saffron *Colchicum autumnale* in the sixth century. Colchicine has no effect on the production or disposition of uric acid, yet it is so specific for arresting an attack of acute gouty arthritis that it is also used, indirectly, as a means of diagnosing the disease.

Although progress has been made in elucidating the mechanism of colchicine action, the precise way in which it acts to halt the acute attack has heretofore defied explanation. Medical science has been equally baffled by the link between two distinctive features of gout; the acute inflammation which recurs in one or more joints of the body, and the metabolic defect which leads to increased concentration of uric acid in the tissues.

The search for clues to these and other elusive factors in gout has yielded more significant information during the past decade than has been found in the studies of all previous eras. Joined in this search with their colleagues around the world, scientists at the National Institute of Arthritis and Metabolic Diseases (NIAMD) at Bethesda, Md., and NIAMD grant-supported investigators at other research centers, have enhanced present knowledge of gout by numerous major contributions. Such contributions include recent observations that there are different basic causes for high serum urate levels among gout patients; in some, there is excessive production of uric acid, while in others, there is diminished excretion of uric acid by the kidney. Both mechanisms lead to increased uric acid levels in the blood and tissues.

URIC ACID INHIBITORS

Past attempts to control the abnormally high rate of uric acid synthesis in gout through the use of certain inhibitory agents have been thwarted because these agents were too toxic for general clinical use. Alhough normal uric acid levels can be maintained in most gouty patients by the use of uricosuric drugs, certain undesirable side effects result from increased urinary excretion of uric acid such as the formation of kidney stones and accumulation of uric acid sludge in the kidneys.

Institute grantees recently reported the results of a study of gouty patients who were treated with a new drug, hydroxpyrazolopyrimidine (HPP), which effectively inhibits uric acid synthesis and appears to be extraordinarily well tolerated. All patients in this study showed dramatic reductions of uric acid concentrations in serum and urine. Moreover, these patients displayed no evidence of untoward effects in their blood, liver, gastrointestinal tract, or kidneys. This compound now merits further trial in a larger number of gouty patients since it may offer special advantages to those with intolerance of, or inadequate response to, uricosuric agents, or to those with kidney complications associated with gout.

RESEARCH

Recently, a team of Institute scientists provided long-sought evidence which demonstrated how colchicine interrupts the painful attacks of acute gouty arthritis. Their studies showed that the drug decreases the metabolic activity of white blood cells which accumulate in the affected area to engulf urate crystals, thereby stopping a cycle of events that leads to the painful inflammatory response characteristic of acute attacks.

This demonstration of colchicines' mechanism was preceded by a series of findings by the Institute team which clarified the role of sodium urate crystals in gout and thereby shed new light on the painful attacks of the disease. The investigators found that sodium urate crystals injected into the joints of volunteer gouty and nongouty subjects produced a specific inflammatory reaction. Noncrystalline urate suspensions did not produce such symptoms.

It was found that therapeutic amounts of colchicine, given prior to these injections, were capable of lessening this inflammatory reaction. Strikingly similar to a spontaneous attack of gout, the positive reactions were found to involve phagocytosis (a defense process in which white blood cells protect the body by engulfing and destroying invading microorganisms and other foreign particles) of the urate crystals deposited in the joints. These findings were a departure from the accepted belief that urate salts are inert substances which have little or nothing to do with the acute attacks of gouty arthritis.

With this explanation of the link between sodium urate crystals and acute gouty arthritis, the team then explored the relationship between colchicine's specific effect on the pain and its ability to suppress the metabolic activity of white blood cells in the inflamed joint areas. Periodic examination of joint fluid taken from patients after treatment with colchicine indicated that the drug reduces the amount of urate crystals which are phagocytozed. This antiphagocytic action of colchicine was demonstrated by a variety of tests which included counting directly the number of crystals ingested by the white blood cells and measuring the amount of carbon dioxide produced by the cells after ingestion of radioactive labeled "urate."

The metabolic activity of the white cells was also determined by measurement of carbon dioxide which the cells produce, when placed in an experimental medium of radioactive glucose. Although carbon dioxide production normally would increase while the cells were phagocytizing, no increase occurred in the medium after the addition of blood plasma from the same subject after he had received a dose of colchicine.

It is known that during the process of phagocytosis, white blood cells increase their metabolism of glucose; one of the end products is lactic acid. In a closed space, such as the joint space, the lactic acid which these cells produce in large amounts during the phagocytosis, will inevitably increase the acidity of the joint fluid with a resultant decrease in solubility of urates and a tendency to further formation of urate crystals. A vicious cycle is thus established where urate crystals initiate joint pain and inflammation, followed by phgocytosis and increased crystal formation, which leads to further inflammation and continuation of the pain. Through its depression of phagocytosis and metabolic activity of the white blood cells, colchicine interrupts this cycle which crystallization of urate in the joint fluid has established.

PSEUDOGOUT

The past year witnessed a provocative report by Institute grantees whose 3-year study of pseudogout, a recently identified member of the arthritis family of diseases, shows that this unique disease stands recognizably apart from other arthritic disorders, including gout. Pseudogout was first described in 1962. Like gout, it is a crystal-induced inflammation of joints which often results in acute arthritis and is characterized chiefly by the presence of calcium pyrophosphate crystals, largely engulfed within the white blood cells in the fluid of affected joints. The group of 30 men and women studied were previously diagnosed as having gout, osteoarthritis, or rheumatoid arthritis. Initial diagnoses of pseudogout were made by X-ray in 18 cases and by joint fluid analyses in 12 cases. Most of these patients had suffered acute arthritic attacks lasting about 8 days. The joint most commonly affected was the knee; in contrast to true gout, the large toe was noticeably not affected. The most frequent associated condition was asymptomatic osteoarthritis. Characteristic calcium pyrophosphate crystals were present in 31 of 32 fluid samples withdrawn from acutely inflamed joints. Thorough aspiration of the affected joints followed by injection of corticosteroids into the joint proved to be the most effective treatment, while colchicine, specifically effective in true gout, was ineffective.

The investigators stated that the cause of pseudogout might be explained by this sequence of events: multiple-minute crystal deposits first occur in joint cartilage in the small open spaces around cartilage cells; death of cartilage cells and the fusion of the deposits follow; then rupture of a deposit into the joint space triggers an inflammatory reaction. The severity of this response varies with the size of the deposit. Attacks are prolonged if deposits dribble into the joint space gradually, but these attacks are explosive and acute if deposits are dislodged quickly.

The new era which has made such striking advances in the study of gout heralds hope for eventual answers to the problems related to a disorder which has tormented mankind for generations. As a result of sound clinical research carried out in recent years, the clinical manifestations of this metabolic disorder can, at present, be reduced to a minimum, and patients with this disease can be maintained with reasonable comfort and need not fear the hitherto disabling and crippling effects of this disease. Indeed, acute and chronic gouty arthritis has become a preventable disease in the 1960's. The basis for future progress in solving other mysteries of gout and of other hereditary metabolic disorders rests on a firm support of research accomplishments and new concepts, such as those produced at this Institute in recent years.

SPECIAL REPORT ON GASTROENTEROLOGY

Significant wide-ranging advances were made during the past year in the field of gastrointestinal disorders by scientists supported by the National Institute of Arthritis and Metabolic Diseases (NIAMD). Among these are new and improved diagnostic, therapeutic, and surgical techniques for pancreatitis, gallstones, and peptic ulcer.

TREATMENT OF PEPTIC ULCER

Duodenal ulcer is a relatively common disease. A significant percentage of productive segments of the population are affected by this disease, and economic repercussions are felt during the long periods of rest required for the medically treated patient, or during convalescence of a patient after surgery.

Last year, in preliminary studies of an unusual therapeutic technique, NIAMD grantees at the University of Minnesota School of Medicine have been able to produce healing of duodenal ulcers in a significant number of patients by a method of supercooling the acid-producing mucosal lining of the stomach for short periods of time. The technique, which involves perfusion of a frigid liquid through a balloon placed in the patient's stomach, presumably results in "physiological gastrectomy" without physical loss of the stomach, and after treatment symptoms and signs of duodenal ulcer have disappeared for periods varying from 8 months to 2 years (the latter being the total time span to date since introduction of this treatment).

Thus far it has been necessary, in some patients, to repeat the gastric freezing treatment to maintain them free of symptoms, while others have remained free of symptoms since the original treatment.

Since the first description of this unique method, which promised to obviate the need for serious and extensive gastric surgery in thousands of patients, many physicians have begun to use it either for purposes of continued clinical investigation and evaluation or as a routine method of treatment. Since adoption of this method, a number of untoward reactions have been reported, especially when the procedure was used indiscriminately or by untrained hands. In the face of conflicting reports on the safety and efficacy of gastric freezing, the Institute has initiated support of a broad scale evaluation of this technique through a cooperative multiclinic study involving five academic clinical centers and one evaluative statistical unit at a sixth university. These studies which are conducted under a common experimental protocol involve 1 year of experimental work with laboratory animals now underway, to be followed by clinical evaluation of the method in patients.

Since initiation of this multiclinic cooperative evaluative study, the University of Minnesota group which originated this unique treatment has released an interim report on results obtained thus far in 365 patients, which appears encouraging in general, but which describes certain modifications in the method and emphasizes the importance of close attention to technical details and to care of the patient.

It is obvious that gastric freezing is a complex phenomenon which depends on many critical technical factors for successful application. Failure to consider and control each factor may impair the effectiveness of the treatment or injure the stomach. For instance, painstaking investigations by NIAMD grantees in animals have shown that it is possible to produce local ulceration in the stomach wall during gastric freezing, an undesirable side effect which has been reported in a number of patients. These investigators have shown that this injury occurs almost without exception at a point at which the jet-thrust of the inflowing cold alcohol solution hits the inside of the balloon and apparently truly freezes (rather than supercools) the adjacent stomach wall. These investigators have shown that such injuries can be eliminated by controlling the position of the infusion tip and by changing its design so that the coolant emerges through multiple pinpoint openings in all directions rather than hitting one location in a concentrated stream.

While the evaluation of this new method continues, gastric freezing must still be considered an experimental method of therapy. Ideally, it should probably remain restricted to university and hospital centers where careful and continued objective assessment of the problem by trained teams will ultimately determine its place in the management of peptic ulcer.

NEW THERAPY FOR PANCREATITIS

Last year NIAMD grantees developed an effective new treatment for pancreatitis, a disease often acutely fatal. The complete pathogenesis of this disorder has never been clearly defined, but premature activation of a protein-digesting enzyme, trypsin, in the pancreas is an important contributing cause of this catastrophic illness.

The grantees tested a new trypsin inhibitor, isolated from the parotid glands of cattle, in experimental animals. Following successful treatment of experimentally induced pancreatitis in laboratory animals, the investigators treated bouts of recurrent, acute pancreatitis in human patients. Relief of the intractable pain, and of the attacks, without side effects was obtained within 20 minutes. Evaluation of the new agent continues at the present time.

SURGERY OF THE GASTROINTESTINAL TRACT

During the past year, Institute-supported scientists were responsible for particularly important surgical developments in the area of gastroenterology. Recent experiment studies have indicated that the stomach and intestines can be added to an ever-growing list of organs which can be successfully transplanted within the body (autografting) and which may retain their original function in the new site.

Much can be gained from studies of such experimental autografts: an increase in surgical knowledge from working with innumerable gastric and intestinal surgical translocations and enhanced knowledge of the physiological functioning of organs under altered conditions. Out of such studies may evolve new treatments for conditions such as ulcerative colitis, enteritis, and peptic ulcer, diseases about which we, as yet, still know all too little.

In this relatively new field, NIAMD grantees recently found that dogs apparently become resistant or refractory to peptic ulcer when their stomachs are removed and reimplanted. Such animals were not subsequently affected by repeated ulcer-producing stress ordinarily sufficient to produce ulcers and kill normal dogs, and they were in good health, 3 years later. This effect was attributed to the transplanted stomach's inability to secrete normal quantities of pepsin, a protein-digesting enzyme believed to play an important role in the production of ulcers. A realistic implication of this work for the treatment of a diseased organ has not yet been determined.

DIAGNOSTIC AID FOR ABDOMINAL DISEASES

In studies designed to improve diagnostic aids of various gastrointestinal diseases, another group of Institute grantees found that determination of ammonia levels in peritoneal fluid may be of distinct value in the differential diagnosis of acute abdominal conditions.

Microbial putrefactive processes in the gastrointestinal tract normally lead to the formation and local accumulation of ammonia. Based on this knowledge, the investigators developed a new diagnostic approach involving measurement of the ammonia content of the abdominal fluid after spillage of intestinal contents attendant to acute intra-abdominal lesions and perforations.

This new diagnostic technique permits differentiation, on the basis of ammonia concentrations in peritoneal fluid, between pancreatitis and hemorrhage due to ectopic pregnancy, ruptured ovarian cyst, or ruptured spleen, on one hand, and perforation of strangulated intestinal loop, appendix, or duodenal ulcer, on the other. Proper interpretation of the ammonia content in the abdominal fluid, obtained by needle, may save the patient the risk of an exploratory operation.

GALLSTONE ORIGIN CLARIFIED

NIAMD grantees have found new evidence to clarify the origin of gallstones. Although cholelithiasis (gallstones) is not an uncommon disease, the question of how stone formation actually begins remains unanswered. Based on studies with experimental animals and patients, the grantees found that bacterial infections caused primarily by Klebsiella pneumoniae, may be responsible for a metabolic derangement in the liver that results in the formation of an abnormal compound, ornithocholanic acid. This compound lowers the solubility of normally present cholesterol and bile pigment in bile, "salts them out of solution," and thus sets the stage for cholesterol and bile pigment to precipitate out of the bile and form the nucleus of a gallstone. The stone would then grow much as a pearl in an oyster, and may cause blockage of the gallbladder ducts or irritation of the gallbladder.

OTHER DEVELOPMENTS

Surgical repair of a damaged sphincter (a valve-like muscle) in the esophagus to prevent acid stomach contents from "flowing back" into the esophagus has seldom been successful. A new surgical procedure developed in experimental animals by an NIAMD grantee has now proven effective in 24 of 29 animal operations.

The new technique, which involves a flap of diaphragm muscle activated by a branch of the nerve which activates the diaphragm was successful in restoring normal sphincter action and in repairing hiatus hernia. There was no postoperative "flowback" and no subsequent failure of sphincter action. In addition, this procedure did not interfere with the normal respiratory function of the diaphragm. Application of the technique to human beings with hiatus hernia has not yet been undertaken.

The diagnosis of pancreatic exocrine insufficiency was facilitated by grantees who developed a stool enzyme activity test that is relatively simple to perform and is more precise than other methods. It involves measurement of the activity of two enzymes, trypsin and chymotrypsin, in human stools, and permits differentiation of chronic pancreatitis and cystic fibrosis from other disorders causing intestinal malabsorption.

The past year has been a particularly productive and rewarding one in the field of gastroenterology with many useful results in several clinical problems and disorders which have long defied investigative efforts. While some of the accomplishments of the past year have found immediate application at the bedside, others, of more basic nature, have contributed to the common fund of biomedical knowledge from which come all advances against disease.

Mr. Fogarty. I think you have covered the arthritis, and diabetes.

ACTIVITY IN FIELD OF HEMOPHILIA

Now, the field of hemophilia. If you listened to the Heart Institute testimony you heard that they are doing quite a bit of research in hemophilia. What are you doing in hemophilia?

Dr. Whedon. Mr. Chairman, we have quite an active program in this general area. You may recall that last year at this time, I gave a brief general description of the various ways in which the clotting process could go on, and I made the point that hemophilia was just one of three main groups of disorders of the clotting mechanism. We prefer to think of hemophilia in its broad sense encompassing several ways in which clotting may be ineffective. But, with specific reference to the classic disease, hemophilia itself, during the past year, the research group within our own Institute in Bethesda has been particularly interested in attempting to obtain manufacture of the particular missing clotting agent in this disease, which is called AHG, antithemophilic globulin, or AHF, antihemophilic factor.

At our present stage of knowledge of this disease, and of awareness of the difficulty in its treatment and management, it is not possible for us to alter the basic disorder. But we believe if adequate quantities of AHG were available, that when the patient with hemophilia comes to surgery, has to have an operation for some reason or another, if the patient could be protected by administration of AHG before, during, and following surgery, then such patients would have a normal course and would not have an unusual degree of bleeding, which of course makes it extraordinarily difficult for the surgeon's work.

MANUFACTURING AHG

Mr. Fogarty. Why are not there adequate supplies of AHG?

Dr. Whedon. This apparently is quite expensive and difficult to develop and with relatively small numbers of patients, it has been difficult to interest people in manufacturing this.

Mr. Fogarty. If they cannot do it, why do you not do it?

Dr. Whedon. This would move us out of the area of research into the area of production of a therapeutic substance.

Mr. Fogarty. Have you not done that before? Has not the Public Health Service done this before?

Dr. Whedon. In other areas——

Mr. Fogarty. I was thinking specifically of the manufacturing of yellow fever vaccine. Is that not right?

Dr. Whedon. Yes, that is correct. Yellow fever vaccine was manufactured by the Rocky Mountain Spotted Fever Laboratory of the Public Health Service from 1941 to 1952.

Mr. Fogarty. Is it not possible for you to use funds for activities to attempt to synthesize AHG and maybe have it produced at lower cost?

I think this was done in the area of cortisone, ACTH, streptomycin, and things of that nature.

Dr. Whedon. I think it is possible. I am not familiar with the actual——

Mr. Fogarty. You could make grants or contract with private organizations to do it?

Dr. Whedon. I think Mr. Chairman, it might depend upon the magnitude of the problem. It might be actually relatively prohibitive in the total amount of funds that would be required from Federal sources for this purpose.

Mr. Fogarty. Let's take a look at what was done in streptomycin in 1947 or 1948 and what was done in cortisone and ACTH, and then compare it with your problem. Put a statement in the record on it, will you, please?

(The information requested follows:)

Additional New Information Concerning Antihemophilic Factor

Very recent developments pertaining to the commercial production of antihemophilic factor (AHF) have clarified considerably the picture of future availability of AHF. In the recent past AHF was only available in commercial fibrinogen preparations. The amount of AHF in these preparations depended to a great extent on circumstantial delays and occasional clotting which may occur between the bleeding station where human blood, the basic raw material, was obtained and the eventual use of the final commercial fibrinogen preparation. These preparations were sold for their fibrinogen content and not for the AHF content which would vary considerably in this material.

Two American pharamaceutical firms are now on record as being ready to produce a preparation which contains standard amounts of AHF, the standards to be set by the Division of Biologics Standards of the National Institutes of Health.

MENTAL RETARDATION RELATED TO NEONATAL JAUNDICE

Mr. Fogarty. Now, you mentioned mental retardation, but I did not get the connection. What was done?

Dr. Whedon. This was in relation to neonatal jaundice. That is development of jaundice in young infants very soon after birth.

What has been accomplished in that area is that we found a new cause for this type of jaundice.

Mr. FOGARTY. How do you connect it with mental retardation?

Dr. WHEDON. Well, the matter there is that if patients remain jaundiced for any lengthy period of time, the bile salts or bilirubin, will tend to collect in tissues, and particularly if they collect in nerve tissues and brain during the period of development of the brain, this will interfere with the normal maturation of the various tissues and mental retardation will develop.

Mr. FOGARTY. Can you say in this discovery you have been able to prevent this kind of retardation?

Dr. WHEDON. Well, for mental retardation of this particular type, that is true.

Mr. FOGARTY. That is what I meant.

Dr. WHEDON. Yes; what was discovered, Mr. Chairman, was that there was a unique steroid substance which was elaborated in the mother's milk. Actually there is a rather complicated story the way this was discovered.

About 2 years ago, a grantee of our Institute examined one of these infants only 2 weeks old for every cause of jaundice that he could find and was unable to determine the reason. He suspected that there might be something in the mother's milk that was causing this, but he exhausted his own originality in trying to determine the reason. But later, he found that another one of our grantees had discovered an unusual steroid substance in the blood of women who gave birth to severely jaundiced infants. Our two scientists got together, communicated very effectively with one another, and they were able to demonstrate that this new substance, which is an unusual hormone, actually inhibits a vital enzyme reaction which ordinarily transforms bile pigment into the form in which it is normally excreted in the urine.

The happy side of this story is that when the jaundice is due to this particular substance, all that has to be done is to take the infant off mother's milk and switch him to regular cow's milk formula and the jaundice gradually clears, and so of course the child will develop normally. But precisely why some women will form this unusual steroid is unknown.

Mr. FOGARTY. Could that be determined at the time of birth?

Dr. WHEDON. Yes, certainly——

Mr. FOGARTY. Is it recognized by the average obstetrician?

Dr. WHEDON. I think it is going to be. It is such a relatively new finding that I am certain that not all pediatricians know it, but the information will clearly be broadcast.

CYSTIC FIBROSIS

Mr. FOGARTY. Now, on cystic fibrosis, Doctor, are you making some inroads on this problem?

Dr. WHEDON. Cystic fibrosis, Mr. Chairman, is one of the diseases which I hinted at earlier that is an extraordinarily stubborn disorder.

Mr. FOGARTY. What does hair have to do with it? Was hair one way of diagnosing it?

Dr. PRICE. Sweat.

Dr. WHEDON. Analysis of sweat is the method by which cystic fibrosis is diagnosed.

I think something was mentioned last year about the hair. At the moment I cannot recall what it was. But I am certain it was not in connnection with cystic fibrosis.

(The following additional statement was subsequently supplied:)

During my testimony last year, Representative Lesinski mentioned analysis of hair in cases of poisoning. Traces of arsenic, for instance, can be found in the hair if the person was subject to gradual arsenic poisoning over a period of time. In addition, various normally present trace metals can now be detected in hair samples and these analyses are being used in clinical studies of trace metal metabolism.

Mr. FOGARTY. All right, will you supply for the record what you are doing on cystic fibrosis?

(The requested information follows:)

SPECIAL REPORT—CYSTIC FIBROSIS

Cystic fibrosis is an inherited, generalized, metabolic disorder affecting the exocrine glands, glands which discharge their secretions onto the skin (sweat glands) or into organs which connect to the outside of the body (lungs, intestines, etc.), either directly or through special ducts.

In cystic fibrosis, the mucus-producing glands fail to secrete their normal, clear, free-flowing fluid. Instead, they produce an abnormal, thick, sticky mucus which tends to obstruct the ducts or openings of the glands. These abnormal secretions lead to a variety of serious complications. When the thick mucus accumulates in the ducts of the pancreas, it interferes with the function of this gland to supply much-needed digestive enzymes to the intestinal tract.

Another complication involves the lungs. Almost all cystic fibrosis patients develop chronic pulmonary diseases at some time during the course of their illness. Thick mucus deposits tend to clog passages in the lung or branches of the windpipe, causing obstructions manifested by labored breathing or a chronic cough. This condition may lead to chronic bronchitis, extreme susceptibility to lung infection, and pneumonia.

Still another basic abnormality is found in the nonmucus secreting sweat, salivary, and tear glands. In cystic fibrosis, the secretions of these glands usually contain an excessive amount of salt. Because of this sweating defect, many patients are unable to conserve salt, especially in hot weather. With excessive sweating this condition may be severe enough to lead to severe weakness or death.

Cystic fibrosis is believed to be due to an inborn error of metabolism. The basic chemical defect is not yet understood, but it is considered to be genetically transmitted. The disease occurs in about 1 in 1,000 to 1 in 2,000 live births resulting in about 4,000 new cases a year in the United States.

Although in the past cystic fibrosis was confined to the pediatric age group by its high mortality in infancy and early childhood, the disease is now recognized with increasing frequency among adolescents and adults. Recent studies have shown that there are far more adults than previously believed who carry a partial genetic endowment for the disease. The studies also have suggested that variants of cystic fibrosis may be responsible for some chronic lung and gastrointestinal disorders in adults usually not recognized as due to cystic fibrosis.

RESEARCH DEVELOPMENTS AND TRENDS

Cystic fibrosis is one of the diseases under intensive investigation at the National Institute of Arthritis and Metabolic Diseases (NIAMD). A current investigation in NIAMD's Pediatric Metabolism Branch concerns the basic defect in mucopolysaccharide metabolism presumably responsible for the abnormal secretory activity which underlies the clinical manifestations of the disease. In order to open new avenues of research on cystic fibrosis, the Branch has initiated a combined immunological and biochemical approach to this problem.

This approach is based on the assumption that the defective, viscous mucus of cystic fibrosis contains an abnormal mucoprotein component which can give rise to the production of immune antibodies when injected into animals. Once having obtained the immune sera from suitable animals, it might then be possible, utilizing a variety of immunologic and biochemical methods, to isolate the supposedly abnormal mucoprotein in children with cystic fibrosis, possibly in their parents, and in other asymptomatic carriers which represent from 2 to 5 percent of the general population.

This study has been initiated and is being carried through in collaboration with the Children's Hospital of Washington, D.C. Immunization of rabbits has been completed and sera obtained from these animals. A number of different fractions from body fluids of cystic fibrosis patients and from organs obtained at autoposy have been and are being analyzed, and significant differences are being found both from the immunological and biochemical standpoint.

In studies with adult cystic fibrosis patients, NIAMD scientists have reported several cases which represent new complications of cystic fibrosis, due to intestinal obstruction caused by the viscous, abnormal mucoprotein secreted into the gastrointestinal tract and the abnormal consistency of the stools themselves. Previous diagnoses of several of these patients had ranged from tumor to gall bladder disease. The pathology, however, was different in the various cases, running from volvulus (twisting or knotting of the intestine) and intussusception (a telescoping of one portion of the intestine into the other) to solid masses of feces which cause obstruction in the intestinal tract. The basic cause in each case was similar, and was found to result from the abnormal viscous intestinal secretions characteristic of cystic fibrosis.

These findings by the Institute scientists have given rise to important clinical considerations relating to the type of treatment, surgical or otherwise, to be used in such cases. These and other developments in diagnosis and therapy are being transmitted to practicing physicians and research workers throughout the country.

NIAMD-supported investigators are also continuing their studies of the possible mechanism of mucus obstruction in the various glandular ducts in the cystic fibrosis patient. These scientists studied the submaxillary gland, the saliva of which offers a unique opportunity for analyzing uncontaminated secretions. Saliva was collected under physiological reflex, as well as drug stimulation, from normal children and adults, and children with cystic fibrosis.

The investigators found that saliva obtained from patients with cystic fibrosis on reflex stimulation showed considerably higher protein and calcium content, as compared with saliva from normal control subjects. There was also a higher protein level in the normal child than in the adult, while children with cystic fibrosis exhibited the highest salivary protein output. Under drug stimplation there was the same general proportionality with the exception that cystic fibrosis-like, partially insoluble saliva appeared in the normal children as well after intense stimulation. This would appear to indicate that the threshold response to stimuli in each of the three study groups is different, and that the normal child, ordinarily with a fairly high salivary protein content compared to normal adults, can produce the cystic fibrosis-like salivary insolubility phenomenon in response to increased glandular stimulation.

These findings suggest that there may be a "quantitative" rather than a "qualitative" alteration of the normal secretory process in cystic fibrosis saliva. Such a derangement could logically be explained as a threshold difference between the child with cystic fibrosis and the normal child either at the receptor glanular site or in any components of the complex system involved in glandular stimulation. The investigators have also postulated that the resulting secretion of abnormally large amounts of organic constituents (not necessarily abnormal and different in chemical composition) may bring about increased viscosity of pancreatic and lung secretions and lead to gradual accumulation, resulting in obstruction of the exocrine gland ducts.

Another group of grantee scientists has reported a new clinical entity with a striking similarity to cystic fibrosis. The syndrome may be readily mistaken for cystic fibrosis since the cases studied were marked by pancreatic insufficiency and failure to thrive, among other manifestations.

Four of the six patients exhibiting the new syndrome were originally considered by the grantee scientists to have cystic fibrosis, but repeated diagnostic tests of the disease showed normal sweating, and the lungs were not affected. Further studies of these cases may provide some new insight of cystic fibrosis itself.

Cystic fibrosis is a complex disease of many disguises. Its multifaceted nature has prompted scientists of many disciplines to study its metabolic and genetic aspects, as well as to find ways and means to treat the disorder. In recent years, NIAMD scientists and investigators supported by the Institute have contributed largely in dispelling misconceptions concerning this disease. Two major misconceptions had been that systic fibrosis is a rare disease, and that it is invariably fatal. Neither has been shown to be true. Promising findings in basic research, as well as new methods of diagnosis and treatment have brought about a more optimistic outlook for cystic fibrosis patients.

TREATMENT OF ULCERS

Mr. FOGARTY. Are ulcers on the increase?

Dr. WHEDON. I cannot answer that specifically.

Mr. Chairman, I think in connection with the ulcer story, you might like to have a followup on what I described to you last year with regard to the new treatment which had been recommended at that time.

Mr. FOGARTY. Freezing?

Dr. WHEDON. Freezing the stomach wall.

Mr. FOGARTY. Yes.

Dr. WHEDON. Now, the way that this treatment works is that a balloon is lowered into the stomach and then filled with a freezing liquid, 80 percent alcohol, at a particular low temperature, circulated through the balloon and out again for a specific period of time. This freezing of the stomach wall actually destroys the acid-producing function of the cells in the stomach. An important factor which tends to bring about ulcers is an unusually high elaboration of acid.

Now, what has taken place in the year since we reported——

Mr. FOGARTY. You can go in the hospital in the morning, have this done, and come out at night, can you not? The same day?

Dr. WHEDON. I am not certain of that, Mr. Chairman, but I know that it is a relatively short period of time. However, one of the things that is coming out, has come out during the past year, is that this procedure must be done very carefully. In fact, we are quite concerned that there might be too much of this casual, very short period of treatment. Although in the centers where this work has been done carefully no deaths have been reported, nevertheless even under the best hands, there have been some instances of bleeding and gastric ulceration. The cooling may actually affect the tissue so seriously that a hole may actually develop in the stomach wall and this of course is far worse.

Mr. FOGARTY. Have any problems developed in Rhode Island? Two hospitals are doing this.

Dr. WHEDON. I am not aware of any difficulties in Rhode Island.

May I tell you, Mr. Chairman, that Dr. Wagensteen, who is the man who first reported this——

Mr. FOGARTY. In Minnesota?

Dr. WHEDON. That is right, at the University of Minnesota. He has been able to review the results of the 2 years he has put in on this, and a total of 365 patients have been given this treatment for a total of 461 freezings. In other words, some of these patients have had the treatment more than once.

What they have found is the great importance of the technical aspects of the procedure, for example, the length of time that the freezing liquid goes through the balloon in the stomach, and the temperature of the cooling solution which must be very precisely managed. The size of the balloon is important; if too large a balloon is used, why, too much area of the stomach will be affected and this can cause difficulty. Also, it is important to keep the patient warm. They have also found that the tip of the tube which produces the cooling fluid has been most important. They are apt to get this ulceration of the stomach wall from the cooling fluid if there were a jet of cool liquid that hits directly. But this can be obviated by changing the tube opening to multiple little openings around the end of the tube.

Mr. FOGARTY. Would you put his report in the record?

Dr. WHEDON. I will be happy to.

(The report follows:)

CURRENT STATUS OF NEW FREEZING PROCEDURE FOR DUODENAL ULCER TREATMENT

Last year, in preliminary studies of an unusual therapeutic technique, NIAMD grantees at the University of Minnesota School of Medicine have been able to produce healing of duodenal ulcers in a significant number of patients by a method of supercooling the acid-producing mucosal lining of the stomach for short periods of time. The technique, which involves perfusion of a frigid liquid through a balloon placed in the patient's stomach, presumably results in "physiological gastrectomy" without physical loss of the stomach, and, after treatment, symptoms and signs of duodenal ulcer have disappeared for periods varying from 8 months to 2 years (the latter being the total timespan to date since introduction of this treatment).

Thus far it has been necessary, in some patients, to repeat the gastric freezing treatment to maintain them free of symptoms, while others have remained free of symptoms since the original treatment.

Since the first description of this unique method, which promised to obviate the need for serious and extensive gastric surgery in thousands of patients, many physicians have begun to use it either for purposes of continued clinical investigation and evaluation or as a routine method of treatment. Since adoption of this method, a number of untoward reactions have been reported, especially when the procedure was used indiscriminately or by untrained hands. In the face of conflicting reports on the safety and efficacy of gastric freezing, the Institute has initiated support of a broad-scale evaluation of this technique through a cooperative multiclinic study involving five academic clinical centers and one evaluative statistical unit at a sixth university. These studies which are conducted under a common experimental protocol involve 1 year of experimental work with laboratory animals now underway, to be followed by clinical evaluation of the method in patients.

Since initiation of this multiclinic cooperative evaluative study, the University of Minnesota group which originated this unique treatment has released an interim report on results obtained thus far in 365 patients, which appears encouraging in general, but which describes certain modifications in the method and emphasizes the importance of close attention to technical details and to care of the patient.

It is obvious that gastric freezing is a complex phenomenon which depends on many critical technical factors for successful application. Failure to consider and control each factor may impair the effectiveness of the treatment or injure the stomach. For instance, painstaking investigations by NIAMD grantees in animals have shown that it is possible to produce local ulceration in the stomach wall during gastric freezing, an undesirable side effect which has been reported in a number of patients. These investigators have shown that this injury occurs almost without exception at a point at which the jet-thrust of the inflowing cold alcohol solution hits the inside of the balloon and apparently truly freezes (rather than supercools) the adjacent stomach wall. These investigators have shown that such injuries can be eliminated by controlling the position of the infusion tip and by changing its design so that the coolant emerges through multiple pinpoint openings in all directions rather than hitting one location in a concentrated stream.

While the evaluation of this new method continues, gastric freezing must still be considered an experimental method of therapy. Ideally, it should probably remain restricted to university and hospital centers where careful and continued objective assessment of the problem by trained teams will ultimately determine its place in the management of peptic ulcer.

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INTERIM REPORT ON RESULTS OF GASTRIC FREEZING FOR PEPTIC ULCER

PRESENT INDICATIONS, LIMITATIONS, AND CLINICAL ACHIEVEMENT

(Eugene F. Bernstein,[1] M.D., Robert L. Goodale, Jr., M.D., Arthur S. McFee, M.D., Arthur J. Madsen, M.D., John P. Delaney, M.D., and Owen H. Wangensteen, M.D., Minneapolis)

Gastric freezing is under evaluation as a definitive treatment of various manifestations of the peptic ulcer diathesis, including duodenal, gastric, and stomal ulcer, and stenosing esophagitis. The vast majority of the 365 patients treated by us to date have been candidates for elective surgery for duodenal ulcer (table 1). Following a freeze of 45, 50, or 60 minutes, with gastric inflow temperatures of about —17° C. (0.8° F.), dramatic and immediate relief of ulcer pain and rapid healing of ulcer craters has been observed quite regularly.

The distinction between gastric cooling and gastric freezing needs reemphasis. Gastric cooling, involving inflow temperatures of 5° to 10° C. (41°–50° F.), has been employed in the emergency treatment of massive upper gastrointestinal hemorrhage since its development in 1958 (1, 2). Its efficacy has been confirmed in a number of independent observations and it appears to have found favorable acceptance by the medical profession.

Gastric freezing, on the other hand, is a newer procedure for the elective and definitive treatment of some manifestations of the peptic ulcer diathesis (3–5). Our experience with gastric freezing, although brief, has been encouraging (6–9). However, the procedure has not been without the trials which beset the clinical introduction of any radically new therapeutic modality. Until gastric freezing has been further studied and reassessed, general employment of the technique should remain limited to those university hospital centers where it may receive critical evaluation and realistic appraisal.

Our own experience currently includes 365 patients who have undergone 461 episodes of gastric freezing with no incidence of mortality. However, the method is still not free of morbidity. Twelve of our patients have developed postfreeze melena and 9, gastric ulcer. Modifications of technique and increased experience have succeeded in identifying and successfully altering some of the factors contributing to these complications. Only time will tell whether it will be possible to eliminate all evidence of morbidity.

TABLE 1.—*Total clinical experience with gastric freezing*

Disease:	*Number of patients*
Duodenal ulcer	286
Stomal ulcer	38
Benign gastric ulcer	16
Stenosing esophagitis	5
Miscellaneous	20
Total	365

This presentation will attempt to redefine the present indications and limitations of gastric freezing and to summarize our clinical achievement in patients with chronic duodenal ulcer and postgastrectomy stomal ulcer. The 18-month period of observation obviously has been too brief to give our conclusions a ring of finality, but the keen interest in gastric freezing appears to warrant an interim report.

TECHNICAL CONSIDERATIONS

Initially, using a gastric hypothermia apparatus with perfusion rates of 650 cubic centimeters per minute, the tolerance of the gastric wall to varying temperatures and durations of freezing was explored. On the basis of studies in over 150 dogs, the initial regimen of an hour's freeze with an inflow temperature of —20° C. (—4° F.) and an outflow temperature of —12° C., evolved (3–5).

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[1] From the Department of Surgery, University of Minnesota Medical School. Dr. Bernstein is a Markle Scholar in Academic Medicine.

Presented as part of the Symposium on Newer Knowledge and Therapy of Peptic Ulcer at the 112th Annual Meeting of the American Medical Association, Atlantic City, N.J., June 17, 1963.

However, the development and employment of freezing machines with higher flow rates (1,500 to 1,800 cubic centimeters per minute) and of larger gastric balloons of thinner latex rubber more suited to the shape of the stomach, was associated with patient morbidity and not experienced in our earlier clinical observations. It has become increasingly apparent that alterations of any of the technical factors involved in gastric freezing necessitate a reevaluation of the entire freezing procedure.

Further studies, including gastroscopic, secretory, and autopsy observations in 64 dogs, served to reemphasize the importance of the following items in the freezing procedure: (1) length of the freezing period—more than 60 minutes is hazardous; (2) balloon distension volumes greater than 600 cubic centimeters in the dog are distinctly dangerous; (3) thickness of the balloon wall—excessively cold areas will result from use of very thin-walled balloons; (4) inflow temperatures colder than —18° C. (—0.4° F.) can be dangerous; and (5) failure to maintain a normothermic systemic temperature during gastric freezing, especially in the dog, can prove disastrous. Clinically, external body warming prevents shivering and minimizes patient discomfort. However, in the considerably smaller experimental animal, the absence of external warming may result in marked systemic hypothermia, ventricular fibrillation, and death. These experimental findings suggest the zone between a therapeutically effective freeze and one causing necrosis of the gastric wall may be narrow but can be defined.

MODIFICATIONS OF TECHNIQUE

Continued reassessment of the freezing technique in the experimental laboratory has resulted in some changes in our clinical freezing procedure. During the summer of 1962, when the freezing time was extended from 45 to 60 minutes, and following conversion of our hypothermia units from low flow rates of 650 cubic centimeters per minute, the postfreeze complications of melena and acute gastric ulceration were observed for the first time. In addition, the jet-thrust projection of the perfusate directed against the greater curvature of the stomach through the single end-hole of the inflow tube was recognized as an important factor in the observed complication of postfreeze gastric ulcer, as emphasized by Dr. Harvey Lippman of Los Angeles. Consequently, the freezing procedure was modified as follows: (1) the duration of the freeze was reduced from 60 to 45 minutes; (2) the end-hole outlet of the inflow tube was sealed and the inflow alcohol perfusate dispersed through many small lateral holes; (3) the temperatures were raised, from an inflow temperature of —20° C. to an inflow of —17° C. (0.8° F.), resulting in an increase of the outflow temperature of from −12° C. to 10° C. (14° F.). The outflow of —70° C. is considered the more important of these temperatures. With these alternations in technique, the stomachs of an additional 74 patients were subjected to gastric freeze with no observed instances of either melena or gastric ulceration.

The present status of the 185 patients with unobstructed duodenal ulcer treated by gastric freezing from the onset of our clinical experience in October 1961 through January 1963 is summarized in table 2. These data indicate that approximately 70 percent of these patients with chronic duodenal ulcer subjected to gastric freezing, who were candidates for surgery, are presently asymptomatic without ulcer medication or dietary restrictions (except alcohol and caffeine). Medical dietary and drug therapy has been discontinued in these patients to permit a more objective evaluation of the relief afforded by freezing. Twenty-two percent of the presently asymptomatic patients have been subjected to more than 1 episode of freezing, and 43 patients (23 percent of the entire group of 185 have had 2 or more gastric freezes.

TABLE 2.—*Gastric freezing for unobstructed duodenal ulcer*[1]

Status	Number of patients	More than 1 freezing	Percent
Asymptomatic	128	28	69
Symptomatic	33	[2] 15	18
Operated upon	14		7.6
Dead (unrelated causes)	2		1.1
No followup	8		4.3
Total	185	43	100.0

[1] All patients treated from October 1961 to January 1963.

[2] 8 of these refrozen for recurrent symptoms without further followup.

MULTIPLE EPISODES OF GASTRIC FREEZING

The place of gastric freezing in the treatment of peptic ulcer disease is still uncertain. Our experience suggests that about 25 to 33 percent of patients will not receive lasting benefit from a single gastric freeze. Longer periods of observation may suggest an even larger number will need additional episodes of gastric freezing. Greater and more protracted secretory depression and histological mucosal changes following multiple episodes of gastric freezing in dogs suggests clinical trial of this approach when a single gastric freeze fails to achieve the desired long-term result. Our limited experience with multiple freezing in man (96 procedures in 71 patients) indicates that it can be performed with relative impunity if the established guidelines are strictly followed. Multiple freezings may therefore have to be viewed as an important aspect of gastric freezing.

Refreezing has generally been performed clinically for recurrence of ulcer symptoms 3 to 6 months following the initial freeze, or if a single freeze has not provided symptomatic relief. The stomachs of a few patients have been refrozen because of failure of a single freeze to significantly reduce high levels of acid secretion (over 100 mEq in 8 hours). A few patients who failed to obtain significant periods of symptomatic relief or depression of gastric secretion are currently undergoing a planned series of gastric freezes at 6- to 12-week intervals to ascertain whether the same prolonged secretory depression will occur in man as attended multiple gastric freezing at shorter intervals in the dog.

SECRETORY STUDIES

Gastric secretory studies the night following the freeze in three groups of patients are presented in table 3. There is some decrease in the incidence and duration of significant secretory depression attending the shorter periods of freezing (45- and 50-minute freeze compared with an hour's freeze).

Secretory data at intervals up to 1 year following a single 60-minute gastric freeze are summarized in table 4. An initial profound secretory depression based on an 8-hour unstimulated overnight gastric analysis was observed in 71 percent of the patients. Within 6 months, all but 11 percent of the patients again have gastric secretory responses in the range of their prefreeze values. It is significant, however, that almost half of the 92 patients whose cases were followed 6 months or more who underwent gastric freeze for chronic duodenal ulcer continue asymptomatic, without ulcer diet or medication, for periods presently extending to 18 months.

TABLE 3.—*Immediate secretory depression following gastric freezing for chronic duodenal ulcer*

INCIDENCE OF ACHLORHYDRIA

	Duration of freeze, minutes		
Secretory test	45	50	60
8-hour unstimulated overnight aspiration (percent)	24	37	53
Peptone gastric analysis (percent)	28	11	52
Hollander test (percent)	30	15	54

INCIDENCE OF PROFOUND SECRETORY DEPRESSION[1]

	Duration of freeze, minutes		
Secretory test	45	50	60
8-hour unstimulated overnight aspiration (percent)	49	54	71
Peptone gastric analysis (percent)	46	31	68
Hollander test (percent)	62	43	75
Number of patients studied	45	89	115

[1] Greater than 50 percent based on total mEq of free acid.

TABLE 4.—*Duration of secretory depression after single 60-minute freeze*

Time for study after freeze	Number of patients studied	8-hour unstimulated overnight aspiration	
		Percent achlorhydric	Percent with greater than 50-percent reduction [1]
1 day	115	53	71
6 weeks	46	7	41
3 months	45	11	33
6 months	19	0	11
12 months	2	0	0

[1] In mEq free acid, compared with patient's prefreeze data.

On the assumption that the previously observed gastric ulcers were largely a result of the jet-thrust effect, in November 1962, we returned to the 60-minute period of perfusion. The stomachs of 42 additional patients were subjected to gastric freezing before a postfreeze gastric ulcer was observed again in a patient who had received 2,000 roentgens of radiation therapy for duodenal ulcer in 1951.

We then retreated to a 50-minute period of gastric freezing. An additional 113 patients since have been subjected to a 50-minute gastric freeze with 1 instance of postfreeze gastric ulcer.

Radiographic studies at the time of freezing commonly indicate the presence of trapped air and fluid in the gastric fundus and antrum which prevents contract between the gastric balloon and mucosa and insulates the mucosa from the freezing process. For this reason, it is our current practice to aspirate all inlying gastric air and fluid with a nasogastric tube after the gastric balloon has been properly seated and filled. Moreover, the gastric freeze is carried out with the patient in the sitting posture to trap any residual air in the very attic of the gastric fundus. The nasogastric tube is removed just prior to beginning the cold alcohol perfusion.

One of the dissatisfactions with the freezing process in both dog and man has been that available balloons have more commonly resulted in freezing of the body and fundus of the stomach than the antrum. We are currently evaluating balloons which may permit more uniform mucosal contact.

The patients tolerance to moderate distension without pain is still the major criterion in determining the volume of alcohol to be placed in the balloon. Average balloon volume is 1,100 centimeters for the adult male. However, variations from 550 to 1,500 cubic centimeters have been encountered. It has been our practice to place a new balloon on each freezing machine each day. A single balloon, therefore, is used optimally only once and then sent to the experimentl laboratory for further use. On occasion a balloon has been used twice and rarely three times.

CLINICAL RESULTS—DUODENAL ULCER

Of the 365 patients subjected to gastric freezing (table 1) (461 episodes of freezing), 286 were treated for chronic duodenal ulcer. These patients represent failures of medical therapy and were largely candidates for surgery on the basis of intractability, previous hemorrhage, or prior perforation with recurrent symptoms. Patients with any degree of pyloric obstruction or gastric retention, as evidenced by greater than 40 percent retention of a 12-ounce barium meal after 60 minutes, are excluded because of the likelihood of augmenting the obstruction by the gastric mucosal edema which occurs during the first few days after freezing. Moreover, prior pyloric obstruction may lead to a postfreeze gastric ulcer. Following an episode of massive hemorrhage an interval of 10 days or more is allowed to intervene before gastric freezing is undertaken.

SURGICAL PROCEDURES

Twenty patients in the entire duodenal ulcer group (286 patients) have been submitted to operation (table 5). Nine of these either would not be candidates for surgery by our indications or would not now be candidates for freezing under our present criteria, since preexisting pyloric obstruction is currently considered a contraindication. Postfreeze melena and gastric ulceration without perforation have always responded to conservative treatment when it is employed. Recurrent or persistent ulcer pain not invariably, but usually, responds to refreeezing.

JAMA, February 8, 1964.

Table 5.—Surgery following gastric freezing for duodenal ulcer (286 patients)

	Number of patients
Operations not indicated by present criteria:	
Postfreeze gross melena	2
Persistent or recurrent ulcer pain	3
Postfreeze gastric ulcer, without perforation [1]	1
Preexisting pyloric obstruction [2]	3
Total (3.2 percent)	9
Operations clearly indicated:	
Recurrent hemorrhage	3
Late evidence of pyloric obstruction	6
Postfreeze gastric ulcer, with perforation	2
Total (3.8 percent)	11

[1] In absence of perforation postfreeze gastric ulcers have been managed successfully and heal rapidly with conservative treatment.

[2] Operation clearly indicated but these patients would not be candidates for freezing under our present criteria.

A positive indication for operation by our current criteria was therefore present in approximately 4 percent of the duodenal ulcer patients submitted to gastric freezing. Among the last 175 duodenal ulcer patients subjected to gastric freezing, only 4 (2.3 percent) came to operation.

During the past year, two additional groups employing our guidelines have joined the gastric freeze effort. Five Minneapolis-St. Paul hospitals constitute the first group and five university clinics the second. As table 6 indicates, 243 patients have been submitted to gastric freezing by the Minneapolis-St. Paul hospitals group. They encountered 12 instances of melena and two of gastric ulcer. The five cooperating university clinics froze the stomachs of 233 patients and experienced 19 instances of postfreeze melena and 3 of gastric ulcer. No mortality attended gastric freezing in either of these groups.

In the overall series, including the University of Minnesota Medical Center experience, 841 patients have been submitted to gastric freezing with no incidence of mortality. Forty-three instances of melena and 14 postfreeze gastric ulcers were observed. The lesser incidence of gastric ulcer observed in these two groups parallels our own more recent experience. In the last 230 patients subjected to gastric freezing at the University of Minnesota Medical Center, only 1 instance of melena and 2 of gastric ulcer have been observed.

TABLE 6.—*Complications of gastric freezing*

	Number of patients treated	Melena	Gatsric ulcer	Mortality
University of Minnesota Medical Center	365	12	9	0
Minneapolis-St. Paul hospitals [1]	243	12	2	0
Other university centers [2]	233	19	3	0
Total	841	[3] 43	[4] 14	0

[1] Minneapolis General, Ancker, Bethesda, St. Joseph's, and Methodist Hospitals.

[2] Chicago Medical School, Columbia-Presbyterian (New York), University of Mississippi, Hahnemann (Philadelphia), and University of Missouri.

[3] 5.1 percent.

[4] 1.7 percent.

STOMAL ULCER

The modifications of technique which have been developed for treating patients with postgastrectomy stomal or marginal ulceration, particularly following the Billroth II subtotal gastrectomy, have been described in detail (10). Of these, the most important is fluoroscopic positioning of a small oval balloon in the gastric pouch.

Our present clinical experience with postgastrectomy stomal ulcer includes 38 patients whose previous operations are listed in table 7. As indicated, 20 patients are now essentially asymptomatic with healed ulcer craters, if such craters were demonstrable prior to freezing.

Table 7.—Stomal ulcer treated by gastric freezing

	Number of patients
Previous operation:	
Billroth II	21
Billroth II, with vagatomy	5
Billroth I	5
Segmental resection and pyloroplasty	1
Gastrojejunostomy	6
Total	38
Present status:	
Asymptomatic	20
Refrozen for persistent symptoms without further followup	5
Died from remote causes	[1] 3
Operated on after two freezes, without relief	1
Less than 2 months since freeze	9
Total	38
Indications for refreezing: [2]	
Recurrent melena	3
Persistent pain and crater	8

[1] One following complications of preexisting chronic pancreatitis without relief of ulcer symptoms.

[2] Three of these patients have had a third gastric freeze, one for recurrent melena and two for recurrent pain.

Eleven patients failed to benefit from their initial freeze. However, in most of these patients, fluoroscopic placement of the gastric balloon had not been employed at the time of initial freezing. These patients have been subjected to refreezing, and 8 of the 11 have since obtained a satisfactory result. Three have subsequently been refrozen a third time because of recurrent melena (1) or pain (2).

This group includes one proven and several suspected cases of the Zollinger-Ellison syndrome in which postgastrectomy melena and ulcer symptomatology have been well controlled by one or more episodes of freezing.

NO DAMAGE TO ADJACENT ORGANS

A number of studies have been performed, both in the experimental laboratory and on the clinical service, to determine the risk of gastric freezing to the function of neighboring vital organs. Electocardiographic tracings have been monitored before, during, and after freezing. Such records show no significant changes beyond those associated with the transient effects of swallowing ice water. There are transient changes in the T wave and ST segment, but not in the ST interval. Such changes immediately revert to normal at the conclusion of the freezing. Similar changes have been observed in animal studies. Several patients with prior myocardial infarcts, and several other with angina pectoris, have been submitted to gastric freezing without any evidence of cardiac embarrassment.

Serum amylase, sulfobromophthalein excretion, and serum glutamic pyruvic transaminase levels have been studied in a number of patients. In none of these has there been any evidence of significant deviation from the normal.

A group of patients has been subjected to periodic measurements of serum vitamin B_{12} level and of B_{12} uptake. To date, patients have been studied at intervals up to 8 months following a single freeze and no abnormalities in B_{12} uptake or decrease in serum B_{12} levels have been detected.

SUMMARY AND CONCLUSION

Gastric freezing, as an elective and definitive treatment for various manifestations of the petic ulcer diathesis, is presently under continuous evaluation and has been employed in a clinical series of 365 patients with no incidence of mortality. Modifications and reemphasis of various technical details include (1) the importance of inflow temperatures no colder than —17° C. (0.8° F.); (2) careful monitoring of the outflow temperature which should be maintained during the freezing procedure at —8° to —10° C. (17.6° — 14° F.); (3) gastric freeze duration of 45 to 50 minutes; (4) avoidance of overdistention of gastric balloon by avoiding painful distention; (5) aspiration of intragastric air and fluid prior to start of perfusion; (6) maintenance of normothermic systemic temperature by external body warming; (7) use of 80 percent alcohol as the perfusing agent; and (8) careful patient selection. Pyloric obstruction constitutes a contraindication to gastric freezing.

Approximately 69 percent of the 185 patients with chronic duodenal ulcer disease treated from October 1961 to January 1963 continue asymptomatic without ulcer diet or medication. However, 23 percent of these patients were subjected to more than one episode of gastric freezing. The results of gastric freezing for stomal ulcer are more impressive, with only 2 failures in 38 patients treated to date. Eleven of these patients have required refreezing to achieve or maintain control of their ulcer disease.

Gastric freezing still must be considered an experimental venture. Ideally, it should probably remain restricted to university and hospital centers where careful and continued objective assessment of the problem by trained teams will ultimately determine its place in the management of various manifestations of the peptic ulcer diathesis.

ADDENDUM

As of December 12, 1963, our series of clinical gastric freezes has grown to 555 patients, with no deaths. Over the past 6 months, the incidence of postfreeze melena remains approximately the same. However, postfreeze gastric ulcer has not been observed since May 13, 1963, since which time 166 patients have been subjected to gastric freezing.

It is to be acknowledged that uniform freezing of the gastric wall is rarely achieved. In a number of instances, a small lead balloon anchored in the duodenum has been used to insure more consistent depression of antral temperature during perfusion. The size of the gastric freeze balloon has been increased to hold up to 1,400 milliliters of alcohol solution. In current practice 1,100 milliliters is the average filling volume of the balloon during perfusion. The rate of perfusion averages approximately 1,600 milliliters per minute. In the laboratory, we are working with machines capable of considerably faster perfusion rates. Use of low molecular weight dextran, 1 gram per kilogram of body weight administered intravenously, to minimize blood sludging in the vessels of the frozen stomach while not lessening gastric secretory depression, has permitted return to an hour's freeze at inflow temperatures of —20° to —22° C. (—4° to —7.6° F.) without augmenting the incidence of postfreeze complications. Outflow temperatures of —12° C. (10.4° F.) are quite regularly achieved within 15 minutes of commencement of the perfusion. During the last 45 minutes of the hour's perfusion, the desired —20° C. inflow is usually achieved. A thermocouple fastened to the external surface of the freezing balloon along the mid-greater curvature indicates that the mucosal temperature is quite regularly depressed during the last few minutes of the procedure to a few degrees above freezing. In 30 percent of the cases, thermocouple readings below —1° to —3° C. (30.2° to 26.6° F.) have been observed.

Whereas the employment of low molecular weight dextran has not eliminated gastric erosions or superficial ulcers in experimental freezing of the intact stomach of dogs, the extent and depth of such lesions, contrasted with controls, have been strikingly diminished.

Of 33 dogs with isolated gastric pouches subjected to balloon or open techniques of freezing 6 to 24 months ago, 9 of the 15 still living remain completely unresponsive to all gastric secretory stimulants. Twenty-four (73 percent) became achlorhydric following a single freeze. Current freezing techniques of the intact stomach of both dog and man fail to approximate this achievement in secretory depression. Open perfusion, done without a balloon and employing a low viscosity nontoxic fluid, theoretically would best meet the requirements of the situation, affording the greatest promise of establishing intimate contact between most, if not all, of the secretory cells in the gastric mucosa. Clinical trial with open perfusion freezing techniques awaits experimental demonstration of the safety and superiority of the method.

Of 164 patients with duodenal ulcer subjected to gastric freezing 1 year ago or more, 83 (50 percent) remain asymptomatic; an additional 18 (10.9 percent) are classified as improved. Of these 101 patients, 26 had more than one episode of gastric freezing. Thirty-seven (22.5 percent) of the 164 patients still complain of pain. Nineteen of these 37 patients have had more than one episode of freezing. Thirty-six of the 164 patients had duodenal ulcer craters demonstrated radiographically. Of these, 23 remain healed (63.8 percent). Recurrence of the crater or failure to heal was observed in 13 of these 36 patients.

Less than 5 percent of the patients have abandoned the gastric freeze program because of dissatisfaction. Eight percent of the entire group of patients with duodenal ulcer disease treated to date have come to surgery; the great majority of these were treated during the first 12 months of the project.

412 SE Union Street, Minneapolis 54455 (Dr. Bernstein).

This investigation was supported by U.S. Public Health Service Grant No. AM–5689 and the Donald J. Cowling Fund for Surgical Research.

The gastric hypothermia apparatus initially used was supplied by the Swenko Research & Development Co., Minneapolis.

The Pioneer Rubber Co., Willard, Ohio, supplied and assisted in evaluation of balloons to permit more uniform mucosal contact.

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Mr. Fogarty. When there is a report like Dr. Wagensteen's, is this report circulated in medical journals or to the Hospital Association to get this information to the doctors and hospitals?

Dr. Whedon. This report that I have just given you is a summary of his article in the Journal of the American Medical Association for February 8 of this year. In other words, it has only been out 2 weeks.

Mr. Fogarty. Do all doctors read all articles in the JAMA?

Dr. Whedon. The answer to that is quite clearly, no.

Mr. Fogarty. Some do not have time, I think.

FELLOWSHIPS AND TRAINING

Now, you fall into the common pattern regarding fellowships and training. You are just barely "holding your own," are you not?

Dr. Whedon. This is correct, sir.

Mr. Fogarty. Fellowships actually fall off a little, from 319 in 1964 to 314 in 1965, and training grants go up a little from 320 in 1964 to 329 in 1965. Are you about to catch up with the need for trained people?

Dr. WHEDON. Mr. Chairman, the answer is no. We feel it is most important to continue the training of young individuals, whether they be M.D.'s or Ph. D.'s, and this is the purpose of our continuing this program.

Mr. FOGARTY. But you are not continuing it in a very progressive manner; you are just about leveling off.

EXPERIMENTAL TRAINING GRANTS

Now, on page 16, you say, "At the beginning of this fiscal year, two experimental training grants became effective." What were these two you refer to?

Dr. WHEDON. It has to do with the experimental program for improving the training of clinical investigators. We think this is a very important program.

Mr. FOGARTY. Yes. I do, too. Please put a full statement in the record.

Dr. WHEDON. We will be happy to.

(The information requested follows:)

NIAMD EXPERIMENTAL PROGRAM OF TRAINING FOR CLINICAL INVESTIGATION

CONCEPT

This new training program is an experimental one to develop more effective ways of training young men and women for careers in clinical research. The existing methods of training medical specialists and research workers have accomplished much, but it is possible that in various ways in certain centers they may be improved upon. The Institute's experimental program of training for clinical investigation will enable a limited number of selected institutions to attempt to revise and strengthen their training methods for clinical investigators and make these methods more responsive to the present needs of medical research.

The purpose of the NIAMD program is to provide a means of strengthening, intensifying, and possibly condensing the training period between the third year of medical school and the third to sixth year after medical school graduation, during which time period the young clinical investigator is developed. For higher quality studies of disease processes in patients the relatively high clinical proficiency now provided by the residency system must be—for certain, selected, highly qualified individuals—impregnated with training experience in high quality laboratory research techniques and procedures and understanding of the sophisticated research method.

THE PROBLEM

"It seems clear to the committee that the manpower report demonstrates that the simple uncritical extension of current training activities is wholly inadequate to deal with the complex and changing circumstances of the future." From comments of the Committee on Appropriations of the House of Representatives on "Manpower for Medical Research" prepared by the National Institutes of Health, February 1962.

The Nation is confronted with the task of providing adequate numbers of individuals in the health professions to care for the present and future health needs of its people. The first step toward this end is the provision of a highly competent cadre of academicians who will provide the necessary educational environment for the larger numbers of physicians required to meet the immediate needs of the public. A related facet of the problem is the continuing desire to seek the cause and master the effect of the diseases which plague mankind throughout the world.

One of the most dramatic and far-reaching changes which has occurred in medical education during the past decade has been adoption by medical schools of staffing patterns which provide for full-time appointment of individuals to positions in clinical departments who are expected to be unusually talented in the exercise of clinical responsibilities, who are capable of imparting their knowledge in an effective way to students, and who are actively engaged in investigative programs which require not only their superbly developed clinical skills, but also knowledge of and experience with the tools and modes of thought of basic scientists.

As pointed out in Manpower for Medical Research, Requirements and Resources, 1965–70, "Research opportunities combined with teaching and/or service responsibilities have become increasingly attractive to M.D.'s." The prevailing pattern for the training of such individuals, however, has been simply to add year upon year of training in various unselected areas rather than to develop the background he will require through a comprehensive study of his special capacity, to nurture his creative abilities, and to foster educational rather than purely training dynamics. This situation has been brought about by a number of factors, not the least of which are the formal degree requirements, specialty board certification requirements, and the organizational structure of most medical educational institutions.

As programs have developed, a relatively standard image of the investigator-teacher has evolved and the approach to training has been defined in rather rigid increments of time spent in separate compartments of study and experience. To be sure, training of the M.D. for an academic career has improved over the past few years, but it is recognized that the approaches need further study and improvement, and the suggestion has been made that the image of the ideal may be becoming somewhat inflexible and too standardized. A major criticism of the present pattern for training young people for the assumption of academic, research, and clinical responsibility in clinical departments is that it is an unduly long process. As an example, by the time an individual comes into possession of a bachelor's degree from college, he is usually about 22 years of age; 4 years of medical school will bring him to the age of 26; a minimum of 3 years of clinical training brings him to 29 years of age. Add 3 more years of research training and he is 32 years of age. By the time he is prepared to assume the full responsibilities of his career, half of his allotted "threescore and ten" is behind him.

It has been disappointing to learn that the addition of skills in a basic science, such as biochemistry, acquired even in a concentrated 2-year assignment, when added to an equivalent assignment in a clinical area, may not result in an individual's being highly competent in either clinical medicine or in biochemistry. Knowledge and experience are parceled out in limited and discrete portions. It is the unusual individual who is able to integrate all of these varied training experiences into a comprehensibly useful approach at this point in his career. His mentors acknowledge that he is unseasoned and immature even at a relatively advanced chronological age, as compared with individuals in nonmedical fields. It is felt that this unimaginative and uneconomical method of training for careers in academic medicine is ripe for review and reconsideration in order to "deal with the complex and changing circumstances of the future."

FACTS BEARING ON THE PROBLEM

Only through participation in research can the modern medical teacher be equipped to provide the precept and the example in the midst of the rapidly expanding body of medical knowledge. Because he must acquire the skills of both the competent physicians and the astute scientist, a tremendous burden of preparation is placed on the individual as well as his institution.

1. *Traditional role of the medical school.*—In the 1959 education number of the Journal of the American Medical Association, 60 medical schools in the United States and 8 Canadian institutions reported new developments and experiments in such areas as administrative organization, medical student selection, curriculum planning and activation, and augmentation of financial resources. According to this report, however, medical schools were not experimenting directly with the curriculum at the graduate level. This is not surprising since the mission of medical schools fundamentally concerns undergraduate training. A strong graduate program, however, has invariably served to strengthen undergraduate departments by association. Support of graduate clinical training has traditionally come from the hospital served, and now graduate research training is supported primarily by Government or private granting organizations.

Related to the problem is the realization that in many medical schools the curriculum and approach to medical teaching could not be considered on the truly graduate level. Certain enlightened faculties have tackled this problem along with the imponderable body of factual modern medical knowledge which must be incorporated in part or in whole in the present-day curriculum. Related also is the question of the cultural background of the modern physician. Conceivably this could grow in importance in the future with the concept that perhaps many future medical problems will relate more intimately to areas of population, preventive medicine, geriatrics and situations of great social and economic implication.

2. *What is meant by clinical investigation.*—The concept of clinical investigation in this context clearly is not limited to what would be considered clinical observation, but includes both basic and applied research conducted on human materials or components thereof. Whether the research, or "clinical investigation," is at the basic level, as defined by Tuve among others, of seeking new laws and new regularities in nature's processes, or at the applied level, the essential quality to be sought is one of excellence. The problem of training for clinical investigation, then, cannot be limited to the means of acquiring techniques borrowed from other fields to be applied to the ailing human.

3. *Identification of appropriate candidates for academic careers.*—To have an end result of quality implies an early identification of potential quality. This calls, then, for means of identification of appropriate candidates at an early age. Comparative studies might show that the early identification of native creativity requires not only identification at the medical school level, but possibly at college or high school level. Under our present format of graduate training programs we identify such individuals most often only after several years of clinical training, and even then we are reluctant to invest in their "research training" until there has been a further trial of quasi-clinical investigative activities wherein they might be observed still further.

4. *The status of graduate clinical training.*—In the domain of standard graduate clinical training, the great debate on the usefulness of the internship will gradually come to an end and needs no elucidation here. Residency training has not changed materially since such programs were expanded at the close of World War II. Hopefully, academic, specialty, and accreditation groups are studying the deficiencies of the present system of residency training, but there will probably be few major changes in the immediate future. It is presently possible, however, particularly in internal medicine, to modify the standard pattern of training in individual situations of merit. This prerogative would be essential to the feasibility of developing a new dimension in training for research careers in clinical departments.

5. *Present patterns of research training for the M.D.*—This leads us to the area with which NIH and, specifically, NIAMD has been concerned in the past, that of graduate research training. Our studies have shown that by and large this has been superimposed upon a basic background of medical school, internship, and 2 years of standard residency training. While it is essential to continue to meet an overwhelming immediate need for clinical investigators through the medium of our existing programs, it is obvious that we are already very late with an intensive study of new approaches to training for academic medicine and clinical investigation. We find, for example. that it is frequently valuable for the research fellow to spend time exclusively in a basic science department. Somewhere along the way the average medical graduate has either forgotten or has completely neglected a grounding in such relatively elementary subjects as calculus and physical chemistry. His biochemistry is weak even for a modern clinician and is of no value to him in pursuit of a research career. Now he is advised to drop other activities and concentrate again on a basic science for a period, but at best he may only acquire a facility to apply certain biochemical techniques in his studies of human disease. It has been questioned whether he can be considered really competent in such a basic science short of pursuing work equivalent to that required for a Ph. D. thesis.

The picture created by this outline of the sequence of relatively unrelated training experiences, which is becoming standard, is one of an individual trained to death, or at least verging on being past the age of intellectual daring, and not necessarily well educated after all. The elements that have a bearing on the problem of appropriate training for clinical investigative careers include (1) timely identification of creativity, (2) problems of the medical school curriculum, (3) problems relating to present-day internship and residency training, (4) the advanced age at which research fellowship experience now begins, and (5) costs in terms of time, manpower and facilities to the individual and the medical schools.

ACTION TO MEET THE PROBLEM

Eighteen months ago members of the staff of extramural programs, NIAMD, contacted a small number of high-quality medical schools, raising the question of interest or concern for the current training process of clinical investigators and inviting ideas and suggestions for new approaches to production of the most important agents in clinical research. On February 16, 1963, a distinguished group of medical educators and senior investigators met at the National Institutes of Health to discuss the matter in its own right and in the light of tentative proposals from five institutions for a new clinical research training regimen. It was the consensus of this group that the problem described indeed exists, that it should be approached on an experimental basis, providing support only to a limited number of institutions which displayed maximal ingenuity and interest in the program, and that continuing evaluation and surveillance should be exerted in order to take greatest continuing advantage of new developments and leads for improved training.

A special review committee was then organized composed of non-Government scientists and medical educators of unusual capacity, imagination, and experience in clinical investigation. A significant consideration in selection of this committee was the intent that they should constitute a continuing body able to review all applications and appraise the development of the program and its preliminary results during an initial cycle of 5 to 7 years. The committee's criteria for recommendation of a grant for approval were as follows: a high degree of originality or inventiveness in the training plan, capacity of the department or departments to provide the diversified, yet intensive training proposed, sufficiently high quality of students and residents so that trainees would be of superior quality and a plan for continuing review and analysis of achievement of the training goals. Only if an applicant institution met these criteria solidly was it felt that an extended investment would be worth venturing in this important new training program. At the beginning of this fiscal year two experimental training grants became effective. One additional new award has been made which will be initiated this year.

SUMMARY

Although it is acknowledged that existing graduate research training programs have accomplished a great deal in the preparation of young men and women for careers in clinical investigation, the methods of training presently available clearly could be improved. Thus, an experimental program of training for clinical investigation has been established by this Institute to study means of better preparing unusually talented young physicians for an extended and more effective research career. To date, through a highly selective process, three institutions have been awarded training grants of this new and unusual type. The broad categorical program responsibilities of NIAMD, including arthritis, dermatology, diabetes, endocrinology, gastroenterology, hematology, metabolism, nutrition, orthopedics and urology, dictate maximal interest on the part of this Institute in improved methods of investigation of human medical problems and in better ways of developing clinical scientists of highest capability.

NEW LABORATORY OF CHEMICAL BIOLOGY

Mr. Fogarty. The increase for your direct operations is mostly for completion of staffing of the new Laboratory of Chemical Biology.

Do you want to say something about this new Laboratory, the activities it supports?

Dr. Whedon. Correct, sir.

This is another instance, I think, of the situation where we feel that when we have a very difficult problem, that more than one group could be put upon it. The head of this new Laboratory—

Mr. Fogarty. Where is it?

WORK ON GENETIC CODE

Dr. Whedon. In building 10 at NIH. The Chief of this new Laboratory is at the forefront of the work on the genetic code. His particular contribution has been that he has made real progress in the synthesis of the enzyme ribonuclease, which is believed to be very important in the unzipping of the complex spiral molecule of DNA. DNA and RNA will enable reduplication from cell to cell of the master plan by which cells are able to reproduce themselves in precisely the same form that they had originally, and by which they can continue to carry out the formation of important proteins and amino acids, which are the basis of all of our enzymes and most of our hormones.

Mr. Fogarty. This is a very important step, is it not, in basic research?

Dr. Whedon. We think that work on the genetic code is very important.

Mr. Fogarty. It is something that is very difficult for the layman to understand.

Dr. Whedon. Yes, sir; it is indeed difficult not only to understand, but also to explain.

Mr. Fogarty. What is the easiest way for me to explain in a couple of minutes what the breaking of the genetic code means?

Dr. Whedon. Mr. Chairman, I think that the way to speak about this most briefly is to say, perhaps, that the manufacture of proteins is probably one of the most important processes in which cells are engaged, because proteins are the key components in the hormones and enzymes which regulate and control all of the biological processes in the body. These processes have to be regulated accurately, precisely, and continuously in perfect fashion. Because if this does not occur in the fashion I have just described, disease, and sometimes very serious disease, will occur.

Now, sufficient progress has been made in the study of the genetic code to the point where it may indeed be possible for us, one of these days, perhaps within the next 10 years, to introduce chemical substances which may alter a defective mechanism of reproduction of proteins.

If I have made myself clear, what I am saying is that, in certain individuals who have a metabolic disease in which the DNA–RNA synthesis of proteins has become deranged, we may be able one day to find precisely the right substance to put in that will correct this defect.

Mr. Fogarty. By that time, will doctors be making that determination or computers?

Dr. Whedon. I hesitate to guess about that, because what seems extraordinarily complex and difficult at this time, work which can only be done in the best equipped laboratories with extraordinary training, may ultimately become relatively simple. Investigators may develop relatively simple tests which will enable us to pick out the defect.

Now, this has already taken place with respect to certain diseases, such as phenylketonuria and galactosemia, for example, about which we have reported to you in prior years.

GALACTOSEMIA

Mr. Fogarty. I know about galactosemia. Can you speak to that?

Dr. Whedon. I think one of the interesting analogies to this problem which might be useful to you in explaining the importance of this genetic code work appeared in a special reprint of Life magazine ("DNA's Code: Key to all Life"; Life magazine, Oct. 4, 1963), which has been issued and is available.

Mr. Fogarty. I read that at the time, but I would have to read it about five times, I think, to assimilate it.

Would you place more details on this subject in the record?

(The information referred to follows:)

Special Report—Molecular Biology

During the past decade a new scientific discipline, molecular biology, has been established. Brief as its history is, this young and perhaps abstruse-sounding specialy has already armed the life sciences with a series of discoveries and concepts of such depth and consequence that 11 Nobel Prizes have been awarded in this area in the past 5 years. This report describes some of the achievements of molecular biology, the role of the National Institutes of Health in them, and the present state of this field.

"They [atoms] move in the void and catching each other up jostle together, and some recoil in any direction that may chance, and others become entangled with one another in various degrees according to the symmetry of their shapes and sizes and positions and order, and they remain together and thus the coming into being of composite things is effected." (The Greek atomist philosopher, Simplicius, in 530 B.C.)

For centuries the study of living things was divided between two disciplines—morphology (the study of form) and physiology (the study of function)—a separation made necessary by the differences in the tools required. Progress was relatively rapid in morphology because it called only for an inquiring mind and simple tools such as knives and probes. The separation of the disciplines was really more theoretical than actual in the early years of biology's development as a science, for physiology consisted largely of anatomists' theories on the functions of the structures they had uncovered. It was not until chemistry and physics had developed that physiology as we know it could emerge from the realm of pure speculation.

As the study of anatomy with the unaided eye was reaching the limit of its possibilities, invention of a new tool, the microscope, opened up a new world for investigation with the revelation of the minute structure of organs and tissues. The microscope, in time, laid the foundation for the development of the cell theory.

Cells, the basic units of biological structure and function, seemed simple enough at first, but, as microscopes and investigational methods improved, it became apparent not only that cells were really rather complex, containing within them structures of unknown function, but, moreover, that cells were able to perform a staggering number of bewilderingly sophisticated tasks. It was not until the advent of the electron microscope, which opened up yet another new world for investigation, that an authoritative exploration of the cell could begin; and, because the resolving power of the electron microscope approaches the dimensions of large molecules, the establishment of the principles of molecular biology was also begun.

Despite the fact that cells vary enormously in size and complexity, they have in common many fundamental processes at the molecular level. Of these the most obvious, when any living cell is observed, is their metabolism, the chemical changes through which energy is produced for the cell's life processes including the continuous production and disintegration of almost all of its physical substructures and chemical constituents. The discovery that the internal environment of living cells is in a constant state of flux is hardly more than 25 years old and yet is essential to understanding biology. Metabolic flux provides cells with the necessary flexibility for response to external stimuli and allows cells to perform their various special functions, such as the manufacture of specific compounds like hormones, the transmission of nerve impulses, muscle contraction, movement, and the like.

The number of biochemical reactions involved in all metabolism is very large. And these innumerable reactions are, in fact, interrelated; they are controlled by one another. The end product of one process is the starting material for the next, and it may inhibit simultaneously the course of a third reaction. Reasonable guesses put the number of metabolic reactions in any given cell at several thousand. One of the many problems of biological research is that, whatever the exact number of metabolic reactions may be, it is so large that it is impossible, at least for the moment, to work out mathematical expressions describing the exact state of the entire system at any one time. On the other hand, the totality of metabolic reactions or interconversions is neither large enough nor random enough to allow a useful statistical treatment.

Metabolic processes do not, moreover, proceed as a disorganized mixture of reactions, but in a highly organized environment. Cells are composed of substructures, each with a highly ordered microstructure of its own, which apparently bring order out of what would otherwise be intracellular chaos.

Metabolism is made possible by biological catalysts called enzymes, which facilitate specific chemical transformations. Enzymes are almost incredibly efficient, especially in comparison with inorganic or other organic catalysts. A good example of this is catalase, an iron-containing enzyme which promotes the splitting of hydrogen peroxide to form water and oxygen. The same reaction can also be catalyzed by iron alone, but only about one-millionth as quickly. Inorganic iron combined with certain organic molecules has a much greater catalytic efficiency, but still far below that of the specific enzyme catalase. A second important feature of enzymes is their high degree of specificity. Catalase will split hydrogen peroxide or other very closely related compounds, for example, but will not attack many other compounds containing similar oxygen-oxygen bonds. This specificity is even more striking for many other enzymes. The reasons that enzymes are both highly efficient and specific are probably related to their relatively large molecular size. They are proteins, made up of many, often hundreds, of small amino acid subunits.

THE GENETIC CODE

One of the major modes of inquiry into the intricacies of metabolism is the study of its transmission from generation to generation. Geneticists, for a considerable time, have assumed that the smallest structural units associated with heredity transmission, the genes, carry the necessary information for replicating a given structure or quality. The genes were known to be associated with the chromosomes (filamentous structures found in the nucleus of the cell) on which they are arranged in linear order. Much more recently, molecular genetics became a branch of molecular biology when it was discovered that the specific function of the genes is to transmit the hereditary information that determines the structure of proteins elaborated by the cell, including, of course, the enzymes. The discovery of the principles involved made by James Watson, Francis Crick, and Maurice Wilkins, garnered for them the 1962 Nobel Prize in Medicine and Physiology and revolutionized biomedical research.

The discovery of the "genetic code," as the method of transmission of hereditary information is generally termed, can be most easily understood if some of its background is known. The study of heredity came into being 100 years ago when a monk, Gregor Mendel, kept a close watch on successive generations of garden peas and concluded that some unit must carry instructions from one generation to another in an orderly, mathematically predictable way. His findings were published in 1866 and almost completely ignored. Three years later, in 1869, an Austrian scientist named Friedrich Miescher isolated a substance from the nucleus of cells which he described as "acidic."

Later, at the turn of the century, Mendel's work was rediscovered and became the foundation of modern genetic theory. His unit was eventually named the "gene" from a Greek word meaning "to be born." As technology improved in the 20th century more facts were learned about genes. Their precise location was found to be on the rodlike chromosomes present in the nucleus of every cell. In conformance with Miescher's work, they were composed of an acidic chemical, deoxyribonucleic acid—DNA.

In 1944, Drs. Oswald Avery, Colin MacLeod, and Maclyn McCarty, of the Rockefeller Institute for Medical Research, discovered that DNA from one type of pneumococcus bacterium could be incorporated into another pneumococcus type which then assumed all the characteristics of the first. This, and other work along similar lines, suggested that DNA was the primary determinative genetic substance of all cellular organisms.

The DNA molecule, like the proteins, is a polymer but is formed of nucleotides rather than simple amino acids. A nucleotide consists of three parts: Phosphorus, the sugar deoxyribose, and—most important for carrying genetic information—purine and pyrimidine bases. There are four such bases in DNA: Adenine, guanine, thymine, and cytosine, abbreviated A, G, T, and C.

By late 1951, all this was known, but the actual three-dimensional structure of the DNA molecule and the way in which it directed cell replication were still open questions. Linus Pauling, of the California Institute of Technology, a grantee of various Institutes of the NIH since 1946, had completed the better part of the research into the forces holding large molecules together—for which he was to recieve the Nobel Prize in chemistry for 1954. His theory, that weak short-range forces between complementary molecular surfaces would prove to be the basis for biological replication, coupled with the fact that Maurice Wilkins, of King's College, University of London, had taken X-ray diffraction photographs of DNA molecules, implied that DNA had a well-defined structure. James Watson, of Harvard, who was then a research student at Cambridge University, and Francis Crick, of Cambridge, felt, therefore, that answers were to be had and set about finding them.

Watson and Crick spent 18 months arranging metal cutouts, representing the four bases, A, G, C, and T, into a model DNA molecule. That model, one of the major achievements of molecular biology, took the form of a two-stranded coil, a double helix, looking very much like a spiral staircase. The supporting sides of the staircase were made up of regularly alternating phosphate and sugar groups. The steps of the staircase are in two parts, each part one of the bases, linked where they join by weak molecular forces. The bases always pair in the same way, A with T and G with C. Hereditary characteristics are determined by the sequence in which the A–T and G–C crosspieces occur. A particular DNA molecule might, for example, contain this sequence:

A–T
A–T
C–G
G–C
T–A
G–C

It, of course, would be several thousands units long, in order to code the extremely complex messages required of it, and it is twisted into a helix. When a cell begins to reproduce itself, the DNA in the nucleus unwinds, the weak molecular forces linking the base pairs relax, and the pairs "unzip":

A–T
A–T
C– –G
G– –C
T– –A
G– –C

The respective "unzipped" single chains derived from the original DNA act as templates and a second complementary chain is formed on each of the "parent" chains from nucleotides available within the cell. The cell then divides into two, each with a nucleus containing identical DNA chains. The problem of how the nucleotides are lined up so that the proper bases pair was solved by Dr. Arthur Kornberg, of Stanford University, a former laboratory chief of the National Institute of Arthritis and Metabolic Diseases (NIAMD).

Dr. Kornberg shared a Nobel Prize for his discovery of DNA polymerase, an enzyme which brings the four bases into proper position so that molecular force can link them into the new chain:

"Parent" chain	"Parent" chain
A–T	A–T
A–T	A–T
C–G	C–G
G–C	G–C
T–A	T–A
G–C	G–C

DNA AND PROTEIN SYNTHESIS

Given that DNA can reproduce itself and carry its genetic message to new cells, how does it convey specific, precise information to the cell's machinery, where the proteins of enzymes, hormones, skin, hair, muscle, blood vessels, and internal organs are manufactured? Crick and Watson suggested that the sequence of the bases in DNA was responsible for coding information. Building on that theory, they and other scientists, many of them working at NIH or supported by NIH grants, have outlined a theory, with a great deal of experimental evidence behind it, of how this is accomplished.

Proteins, as was said before, are polymers consisting of chains of amino acid subunits. Short chains or chains that lack full protein activity are called polypeptides. Polypeptides often combine to form complex proteins. The protein hemoglobin, for example, which carries oxygen in the blood, is composed of 4 polypeptide chains, each containing about 150 amino acid subunits. All of the proteins are built up from about 20 different kinds of amino acids. Each chain must have exactly the right structural sequence of amino acids to make biological sense, just as a written sentence must have the right sequence of letters, spaces, and punctuation, to convey the intended meaning to the reader.

It should be added, parenthetically, that a significant change in the biological properties of a protein can be wrought by the substitution of just one amino acid. This was demonstrated by Linus Pauling and Harvey Itano, the latter currently with NIAMD's Laboratory of Biochemistry and Metabolism, some years ago. They found that such a defect was responsible for the common hereditary disease-sickle-cell anemia, which causes the red blood cells to stiffen and become sickle-shaped, preventing them from carrying adequate oxygen through the bloodstream to body tissues. Vernon Ingram, an NIAMD grantee, showed further that the substitution of one amino acid, valine, for another, glutamic acid, at one particular point in a protein chain several hundred amino acid units long, was the specific cause of the disease. Further studies, clarifying the mode of action of the defect for purposes of possible therapy are currently being conducted by Makio Murayama and others at NIAMD.

Obviously, an enormous number of different proteins can be constructed from the 20 amino acids; in the same way that an infinite number of sentences can be composed of the 26 letters of the English alphabet. The critical problem of genetic coding is the way in which the sequence of the four bases in DNA can specify a sequence of amino acids in a protein to be elaborated by the cell.

RNA, THE MESSENGER

Since DNA resides inside the cell nucleus, the coded genetic message must be conveyed out of the nucleus into the surrounding cytoplasm where most protein synthesis takes pace. This is analogous to conveying production instructions from the plant manager's office to the factory floor where the production machinery is located. Evidence indicates that the messenger for this transfer is RNA, ribonucleic acid.

Like DNA, RNA consists of chains of nucleotides containing phosphorus, the sugar ribose, and four bases, arranged in a fashion similar to DNA. Three of these bases—adenine, cytosine, and guanine—are identical to those of DNA, but instead of thymine, RNA contains uracil, abbreviated U.

It is generally believed, on the basis of experimental evidence, that DNA contains the "blueprint" of a protein and RNA carries the message that tells the cell how to manufacture it. DNA is simply the master template; exact copies can be made from it, as from a tape recording, and, like a tape recording, its information can be used over and over again.

DNA's method of unwinding, splitting, and pairing the bases of the parent chains with new bases to complete the molecule, suggests a way in which genetic information could be transmitted to messenger RNA: DNA could direct the synthesis of RNA in a manner similar to its own reproduction; the coded instructions for protein synthesis contained in the structure of the DNA molecule could be transferred to RNA by the pairing of RNA bases with the bases in the DNA chain. The RNA could then carry its instructions from the nucleus to the particles in the cytoplasm called ribosomes, the protein-producing machinery of the cell.

Visible only in the electron microscope, ribosomes are round in shape and composed of protein and RNA (called ribosomal or microsomal RNA) in about equal amounts. That they play an important role in protein synthesis has been suspected for some time but it was thought that they functioned as individuals, in isolation from one another. Quite recently, however, with the aid of a grant from the National Cancer Institute (NCI), a group of scientists at the Massachusetts Institute of Technology, under the direction of a former NIH section chief, Alexander Rich, found that ribosomes collect in groups called polyribosomes and work together as if they were integrated machines on an assembly line.

At the ribosomes, messenger RNA acts as a mold, or a template, on which amino acids are ranked in proper order to be manufactured into chains of protein. This theory—RNA as a template for protein synthesis—has been subscribed to for several years and recently has been confirmed in experiments which demonstrated that messenger RNA acts indeed as a template that determines the sequence in which amino acids are linked together in protein chains.

Speculation on how amino acids are brought to the ribosome led a number of scientists to propose a few years ago that an adaptor molecule of some sort might be involved. In 1957, researchers in several laboratories discovered a type of RNA that was much smaller than messenger RNA, and recent experiments based on that finding have identified this new RNA as the hopothesized adaptor. Because of the adaptor's special function and chemical characteristics, it is called either transfer or carrier RNA.

The actual production of protein begins when transfer RNA molecules, one for each of the amino acids, pick up amino acids in the cytoplasm and carry them to the polyribosome. The amino acids are properly alined on the template RNA, apparently by the mating of a particular group of bases on each strand of transfer RNA with a complementary group of messenger RNA bases on the polyribosome.

The first clear insight into the actual cryptography of the genetic code was obtained by Marshall W. Nirenberg and J. Heinrich Matthaei, of NIH, with an experimental system using the protein-synthesizing machinery of *Escherichia coli*—the common colon bacilli, often called the "white mice of the test tube."

The *E. coli* experimental system contained the 20 basic amino acids as raw materials, adenosine triphosphate to supply energy, ribosomes, and cytoplasmic fluids, the latter two from the bacterium, as the machinery. To this mixture they added a simplified, synthetic RNA, containing only one base—uracil. This simple RNA was to serve as the source of instructions for the building up of a new protein from the amino acids furnished. Out of all the available amino acids, the uracil-base RNA selected only one amino acid, phenylalanine, and used it to synthesize a protein molecule. Drs. Nirenberg and Matthaei knew then that they had determined the nucleic acid coding for a simple protein chain composed only of phenylalanine units.

Within a few months, the two scientists had determined the code for the production of other simple proteins, each composed of multiple units of one or another of the amino acids. Also active in this work was another scientific group at New York University, supported by NIAMD and headed by Dr. Severo Ochoa, who won a Nobel Prize in 1959 for his discovery of the enzyme that hooks RNA parts together.

Akira Tsugita and Heinz Fraenkel-Conrat, of the University of California, grantees of NCI, later showed, in collaboration with Niremberg and Matthaei, that the genetic code may constitute a common "language" understood by all living things. When viruses infect a cell, they place their own genetic material (in some small viruses this is RNA rather than DNA) into it, rendering the cell unable to replicate itself and capable only of producing copies of the virus. Using tobacco mosaic virus, Tsugita and Fraenkel-Conrat extracted some of its RNA and introduced this viral RNA into the bacterial protein-synthesizing system of *E. coli.*

The result was a 75-fold stimulation in protein synthesis, at the direction of the viral RNA. Evidence of marked structural similarity between proteins synthesized by the E. coli system and by tobacco plant cells, under the direction of the same viral RNA, clearly indicated that the genetic code is quite similar for widely divergent living organisms (since instructions from the same virus were needed in similar fashion by a bacterium and by a plant) and thus may be universal. Dr. Elizabeth Maxwell of NIAMD and other scientists have further demonstrated the possibility that the code is indeed universal in experiments with mammalian tissue.

Leon A. Heppel, Chief of NIAMD's Laboratory of Biochemistry and Metabolism, formerly associated with the Nobelist Dr. Kornberg, has been cited for his work on the use of enzymes to determine the structure and metabolism of RNA. With Severo Ochoa, and later with other associates, he studied the formation of "synthetic RNA" by a special bacterial enzyme. These synthetic RNA's may contain only one, two, or three bases instead of the usual natural four. These new experimental tools have greatly simplified the study of the coding problem.

Other molecular biologists, meanwhile, have uncovered more information about the genetic code. One notable achievement was the isolation of a minute quantity of RNA from the T4 bacteriophage (a virus) by E. K. F. Bautz and NIAMD grantee B. D. Hall at the University of Illinois. Analysis of its composition, now taking place, would greatly aid the further cracking of the code. Scientists at the Rockefeller Institute have reported isolation of the messenger fraction of RNA from a mammal, the calf. This particular form of RNA may be the mammalian equivalent of the only messenger RNA that has been available heretofore for study, bacterial RNA.

As genetic code work now stands, there is a general feeling that the beginning of a new era is being reached. Few of the details of the code have yet been worked out and new vistas and accomplishments lie ahead. Although it is known, for example, that the code requires "words" composed of three bases to specify particular amino acids to be incorporated into new protein molecules, only the code triplets for a few of the amino acids have as yet been discovered.

One of the major difficulties complicating the cracking of the code is our limited knowledge of protein structure. Research in this area has advanced to the point where the order in which amino acids occur in some proteins of biological importance has been determined. Broad NIH grant support of many scientists working in this area has resulted in the elucidation of the structure of such important proteins as the hormones, insulin, and ACTH. In fact, with this knowledge, other NIAMD grantees have been able to synthesize these proteins from their component amino acids. The application of X-ray crystallography by J. C. Kendrew and Max Perutz of Cambridge to myoglobin, an iron-bearing muscle protein, and hemoglobin, an oxygen-carrying protein of the blood, has yielded their complete three-dimensional structure. The importance of this work is indicated by the fact that, for it, Kendrew and Pertuz received the 1962 Nobel Prize in Chemistry. These represent only two of the multitude of proteins in the human body, however, and, as Kendrew points out, "we have pressing need to know the structures of very many others * * * we have merely sighted the shore of a vast continent waiting to be explored."

The beginning of this new era may produce a shift in emphasis, a shift from the development of a sound theory to the details of its application. Crick has commented that we must study the more intricate aspects of cell biology. One of the most immediate problems is gene control—what decides whether or not a gene shall act. Genetic studies of bacteria have shed some light on this, but practically nothing is known of the biochemistry of the process. The trail will lead eventually from control mechanisms in single cells to the interactions between groups of cells and finally to the whole process of embryological development. On the way, more must be learned about cell membranes, how the active transport of molecules takes place through them, and how the surfaces of different cells interact.

Work on the intricacies of cell structure has already had an auspicious beginning with the discovery that the mitochondria—tiny, hollow, rodlike structures found in all cells—house the cell's principal energy-producing systems. In the mitochondria, energy is produced in the form of adenosine triphosphate, ATP, a reactive molecule which furnishes energy for most of the energy-using reactions in the cell. (ATP provides, for example, the energy for cell division, DNA replication, and protein synthesis.) The mitochondria house enzyme systems which convert raw material furnished by food, carbohydrates, fats, and, to a lesser extent, proteins, into the energy needed by the cell. An enzyme system as active as that in the mitochondrion, however, soon wears out and requires replacement. To rebuild the system, proteins, vitamins, and minerals are required; this is why these substances are so essential to human health. It is interesting that nutritionists were aware of the importance of these substances long before their precise function was discovered. In fact, the precise metalobic role of a few of the vitamins remains to be fully defined.

Molecular biology and NIH

The NIAMD and the National Institute of Neurological Diseases and Blindness (NINDB) have active laboratories of molecular biology; in addition, research is carried on at several of the other institutes of the NIH concerning separate. though related, problems of the genetic code, protein structure, cell structure, metabolism, and others.

In addition, NIH grants for support of research directly concerned with molecular biology or closely related to it, number in the hundreds. Many of the triumphs of molecular biology have been achieved by NIH grantees and many of the triumphs to come are likely to be the direct result of such support, or will be based on previous findings facilitated by NIH research support. The knowledge to be gained is vital, the new territory to be opened up vast, and the horizons infinite. Man and many of his diseases will remain enigmas until we have the precise understanding of the microstructure of his body that molecular biology can in time give us. The pioneering work on DNA, RNA, and the genetic code, though it has revolutionized biomedical research, is just one aspect of the work of molecular biology. And the potential and implications of even these early accomplishments are enormous.

Dr. WHEDON. I think an interesting analogy in the Life magazine report is that we have reached the stage in this work where it is as though we were like Martian scientists who had been studying the earth and, for many years under the type of magnification available to us, we had found that the earth was occupied by areas which were identified only as villages and cities; then with improvement in our techniques, we had found out that these cities were occupied by beings which moved around and were actually alive. Now we have reached the point of discovering that these various moving individuals were communicating with one another, they were able to converse, and that they had a language that was made up of various key words or codes by which they could communicate among themselves.

Now, the Martian scientists would ultimately find out we had a 26-letter alphabet. Actually our alphabet varies in number of letters with different languages. What scientists have discovered is that there is a 4-letter alphabet which enables the directing mechanism of the protein reproduction process in the cell to tell precisely what kinds of proteins to make, just what the amino acid makeup should be, etc. Although 4 letters may seem like a small number of characters for an alphabet, actually with permutations and variations in 4 letter combinations, one can make all kinds of directions for precise and perfectly reproducible substances. So this analogy may be useful in describing our progress.

We are at the point of trying to find out just what combinations of these four letters will direct the formation of this amino acid or that amino acid.

Mr. FOGARTY. Mr. Denton?

Mr. DENTON. Your estimate is half a million dollars less than was appropriated last year, in round numbers.

Dr. WHEDON. That is correct, sir. I would point out, however, that if the transfer of $5,980,000 to the new Child Health Institute in 1964 is considered, then the adjusted appropriations would reflect an increase of $5,477,000 in the 1965 estimate.

UNOBLIGATED BALANCES

Mr. DENTON. Now, last year, we appropriated $113,679,000. Of that, how much is unobligated?

Dr. WHEDON. As of December 31, approximately $49 million is obligated.

Mr. DENTON. Now, why has so little of that been obligated?

Dr. WHEDON. This has to do with the system by which the funds are expended through the course of the year.

Mr. DENTON. Do you mean your council has not approved the projects?

Dr. WHEDON. No; it merely means that a certain proportion of projects have been approved at the June council meeting and then in November and then we are instructed to expend the funds in a definite sequence throughout the various fiscal quarters throughout the year.

Mr. DENTON. Now, you have $74,244,000 for research. How much of that has been obligated?

Dr. WHEDON. Just short of $42 million.

Mr. DENTON. When does your council meet?

Dr. WHEDON. **The next meeting is in the second week of March.**

Mr. DENTON. Do you know how many projects you have to pass on?

Dr. WHEDON. That information is available. I do not have it here today.

Mr. DENTON. Do you have enough one, two, and three projects to use all of that money?

Dr. WHEDON. It is my estimate that we probably—I am certain that we will expend the funds which have been released to us thus far for the remainder of the year and, as we were discussing earlier, there is a reserve of approximately $1.5 million.

DIFFERENCE BETWEEN RHEUMATOID AND OSTEOARTHRITIS

Mr. DENTON. What is the difference between rheumotoid arthritis and osteoarthritis?

Dr. WHEDON. Osteoarthritis, as we were discussing——

Dr. DENTON. You said that is deterioration, old age?

Dr. WHEDON. It is related to that process. It is not known that any specific substances bring about this disorder.

Rheumatoid arthritis, on the other hand, affects different joints, usually the larger joints of the body—wrists, ankles, shoulders, and so forth—in a different way, so that as one examines the joints, there is a quite clear difference in their appearance and evidence of inflammation, and so on.

It also occurs, or may occur, in much younger individuals and we believe is due to several specific possibilities. One is that there may be an autoimmune reaction whereby the body, in its various glands which develop antibodies whose purpose is to fight invasive agents, may misrecognize some of the body's own tissue substances, think that they are a foreign substance, create an antibody which then reacts with this substance of the body itself and the resulting reaction results in disease.

Mr. DENTON. You mean the antibodies cause the disease?

Dr. WHEDON. The antibodies in combination with the substance which the body thinks is foreign and really is not.

Mr. DENTON. What I am getting at, is it caused by a virus?

Dr. WHEDON. This is a possibility which has just recently developed. There is a disorder which has recently been found in an animal known as the Aleutian mink, whereby the tissues of this animal have many of the characteristics of rheumatoid arthritis. The interesting thing is that this disease in that particular animal is caused by a virus or viruslike organism.

Mr. DENTON. It could not be caused by trauma?

Dr. WHEDON. Fairly definitely the answer to that would be "No." There is a different form of arthritis caused by trauma. It is arthritis, but what we call traumatic arthritis, and it may involve actually more than just the joint; it may involve the ligaments surrounding the joint.

Mr. DENTON. Something besides arthritis, that is?

Dr. WHEDON. That is correct.

Mr. DENTON. Now, several years ago when cortisone was first discovered, we were told by your agency that that was the cure for arthritis. People who had suffered for years would now have a cure and we would not be bothered with this.

That prediction has not been fulfilled; has it?

Dr. WHEDON. No; it has not. Although the effects of the corticosteroids have indeed been miraculous in many cases of relatively great severity, dosages of the steroid had to be given which then caused other effects which were almost as severe as the disease itself, and that has been the problem.

The corticosteroids remain an effective an useful part of our armamentarium against this very serious disorder, but we now know that the steroids have to be given in appropriate modest dosage and the patient very carefully observed for these side effects.

Mr. DENTON. No further questions.

BURSITIS

Mr. LESINSKI. Is not bursitis a form of arthritis?

Dr. WHEDON. Bursitis is closely related, but actually by definition it means inflammation of a bursa, which is a protective bit of tissue which is around the joint but is not specifically part of the joint. In that respect, it is not technically arthritis.

Mr. LESINSKI. In your investigation of Indians of the West on arthritis that you found not hereditary, we should have expected that a long time ago. We all descended from the basically same line of humans; our forefathers thousands of years ago had arthritis. I am sure your proof is fine, but you should have thought about that earlier.

GOLD SALTS

Gold salts, what is it? What kind of salt do you use?

Dr. WHEDON. Well, all I can say to you is that it is a compound of gold in combination with cationic groups, much as sodium or potassium or other elements will combine—I can supply for you the name of the material which is combined with gold, but I do not know.

(The information requested follows:)

Gold sodium thiosulfate.
Gold sulfide.
Gold sodium thiomalate.
Gold thioglucose.
Gold thioglucoanalide.

With the exception of the first two gold salts, the other compounds are combinations of gold and organic sugar molecules.

Mr. LESINSKI. I asked the question because in my mind I cannot envision the body assimilating gold. I know lead is poisonous to the body. Iron per se is not absorbed by the body except in certain form. I imagine gold is the same thing.

Dr. WHEDON. That is quite true. The acceptability of any element by the body depends a great deal upon the other substances with which it is combined when it is introduced.

Mr. LESINSKI. Yes; well, in other words, it is not pure gold?

Dr. WHEDON. No; it is in combination with other materials.

Mr. LESINSKI. Thank you, Dr. Whedon.

That is all, Mr. Chairman.

Mr. FOGARTY. Is there anything else you want to say before we recess?

Dr. WHEDON. I do not believe so.

Mr. FOGARTY. We will come back at quarter past 2.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. JUSTIN M. ANDREWS, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DR. STUART M. SESSOMS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

KENNETH H. BROWN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

M. J. FULLER, BUDGET OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Object classification

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
11 Personnel compensation:			
Permanent positions	4,272	4,792	4,984
Positions other than permanent	53	56	56
Other personnel compensation	137	170	154
Total personnel compensation	4,462	5,018	5,194
12 Personnel benefits	539	591	603
21 Travel and transportation of persons	225	291	298
22 Transportation of things	73	75	80
23 Rent, communications, and utilities	125	113	118
24 Printing and reproduction	4	7	7
25 Other services	4,892	5,768	5,805
Payment to National Institutes of Health management fund	4,214	4,540	4,739
26 Supplies and materials	1,230	1,192	1,254
31 Equipment	367	185	185
41 Grants, subsidies, and contributions	46,277	49,164	50,188
Subtotal	62,408	66,944	68,471
Deduct quarters and subsistence charges	26	26	26
Total obligations	62,382	66,918	68,445

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	682	709	720
Full-time equivalent of other positions	8	8	8
Average number of all employees	652	683	692
Employees in permanent positions, end of year	636	691	702
Employees in other positions, end of year	25	16	16
Average GS grade	7.0	7.3	7.3
Average GS salary	$6,531	$7,027	$6,975
Average salary of ungraded positions	$4,653	$4,725	$4,725

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	37, 562	38, 239	38, 973
(*b*) Fellowships	2, 487	2, 976	2, 976
(*c*) Training	6, 228	7, 949	8, 239
Total, grants	46, 277	49, 164	50, 188
2. Direct operations:			
(*a*) Research	10, 115	11, 174	11, 615
(*b*) Collaborative studies	1, 415	5, 285	5, 285
(*c*) Review and approval of grants	860	995	1, 047
(*d*) Program direction	282	300	310
(*e*) Rocky Mountain Laboratory facility	660		
Total, direct operations	13, 332	17, 754	18, 257
Total program costs, funded [1]	59, 609	66, 918	68, 445
Change in selected resources [2]	2, 774		
Total obligations	62, 382	66, 918	68, 445
Financing:			
Comparative transfers to other accounts	1, 611		
Unobligated balance brought forward	−92		
Unobligated balance lapsing	2, 236	199	
New obligational authority	66, 137	67, 117	68, 445
New obligational authority:			
Appropriation	66, 142	68, 723	68, 445
Transferred to—			
"Operating expenses, Public Buildings Service," General Services Administration (76 Stat. 728)	−5		
"National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−1, 606	
Appropriation (adjusted)	66, 137	67, 117	68, 445

[1] Includes capital outlay as follows: 1963, $482,000; 1964, $185,000; 1965, $220,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders; 1962, $1,493,000 (1963 adjustments, −$24,000); 1963, $4,243,000; 1964, $4,243,000; 1965, $4,243,000.

Mr. FOGARTY. The committee will come to order.

We have now the request for appropriations for the National Institute of Allergy and Infectious Diseases.

GENERAL STATEMENT

Dr. Andrews, we are glad to see you back again.

We shall place your statement in the record and ask that you summarize it for us.

(The statement referred to follows:)

Mr. Chairman and members of the committee, as the lineal descendant of the old Microbiological Institute and its forerunners, the National Institute of Allergy and Infectious Diseases has for more than three quarters of a century been engaged in the search for a better understanding of infectious agents, of their behavior in the animal host, and of means for their control. Because of the relationship between the phenomena of immunity and the reactions of hypersensitive individuals, there has been added to the mission of the Institute in recent years the further responsibility for investigating the nature of allergy and determining the means most suitable for dealing with it.

In carrying out its mission, this Institute, along with exerting concentrated efforts to develop new knowledge and to devise new techniques and new approaches to infectious and allergic diseases, is playing an increasing role in training future medical research workers through the clinical associate and research associate program. In learning modern methods of research in infectious and allergic diseases, young physicians, selected for their competence and interest, work under preceptors. They are trained to conduct careful clinical evaluations of patients, to apply laboratory techniques, to measure physiological and pathological functions, to conduct experimental investigations in animals, to design experiments and studies, and to evaluate results for meaningful reports. The Institute increasingly finds itself a means for preparing young scientists for teaching and research positions in universities and medical schools in this country. NIAID also serves as a training unit for many foreign visitors and guest workers who come to its laboratories to learn the most recent techniques and concepts in allergic and infectious diseases.

Since the development of knowledge itself begets the formulation of new problems, almost all Institute programs are of a continuing nature. In 1963, NIAID research advanced the state of the art significantly in virology, parasitology, bacteriology, mycology, rickettsiology, and allergy immunology.

VIROLOGY

Research on the role of viruses in the production of disease has become one of the leading activities of the Institute. In 1963, NIAID investigations ranged from experimental studies of living cells infected with viruses to epidemiological surveys of virus-connected respiratory illness.

Virus research is complex and varied

Since the end of World War II, knowledge of viruses has increased at almost a geometric rate. The growth of this knowledge has been accompanied by the need for increasingly complex tools and the mastery of varied disciplines required for the study of these agents. We have learned, for example, that the molecular structure of viruses holds a storehouse of information on how agents influence the biological functions of living cells. Yet, virus particles, because they are extremely small, are not easy to visualize, even with the aid of sophisticated instrumentation, including the electron microscope. Virologists are thus required to apply the fundamental principles and methods of biophysics, biochemistry, and genetics in their attempts to uncover the secrets of the elusive viruses.

Virus-related investigations were conducted in many Institute laboratories and in grant-supported and collaborative programs. Among other projects underway in 1963 were the development of prototype vaccines against respiratory or other diseases associated with viral infections of man, initial production of virus reagents for use as research reference materials, and investigations of arthropod-borne viral illnesses. In continuing studies on the infectious and immunologic behavior of viruses known to cause tumors in animals, Institute virologists achieved significant technological and conceptual breakthroughs that may make it possible to show that human cancer, although completely free of infectious virus, contains specific viral antigens.

Research in respiratory disease

Institute scientists conducted investigations using small-particle aerosols to inoculate volunteers with certain viruses as part of the search for effective viral vaccines. Other volunteers were given a mild, protective illness by adenoviruses administered in capsules that dissolved in the large intestine. In another study, a conventional, inactivated rhinovirus containing ECHO 28 virus proved protective against experimental viral illness.

Mycoplasma pneumoniae, a pleuropneumonia-like organism (PPLO) formerly known as Eaton Agent, is responsible for primary atypical pneumonia. It was the subject of several studies, including one intended to produce a living, attenuated vaccine.

It should be emphasized that we are only at the beginning of our effort to control acute respiratory disease. With numerous agents to conquer, we clearly require continued large-scale support for the development and testing of man vaccine components required for eventual prophylaxis against respiratory infections.

The virus reagents program

Of increasing importance to the work in viral respiratory disease is the virus reagents program, established to support research in virology by making available standardized reagents (antigens and antisera) for numerous agents important in human infections. In 1963, laboratories of 13 different organizations, including pharmaceutical companies, university medical centers, and research foundations, took part in the various phases of reagents production, processing, and testing. Disease agents of especial interest were the adenoviruses, influenza and parainfluenza viruses, picornaviruses, arboviruses, herpes viruses, and miscellaneous agents such as Mycoplasma pneumoniae, psittacosis virus, vaccinia virus, and the rickettsia of Q and spotted fever. Antigens and antisera were prepared for a number of these agents. Isolations of new strains continued to be made in each of the virus groups. A contract was awarded for the establishment of a reagent storage and distribution center.

Chronic virus infections

Most known viral diseases are acute. They produce symptoms in the host within a few days, or at most a few weeks, and generally terminate quickly, with either death or recovery of the host. This is the familiar pattern in such diseases as influenza, measles, smallpox, and numerous other viral infections of man and animals.

Within the last few years, however, evidence has been accumulating rapidly that suggests there is another group of diseases caused by viruses that manifest their presence only after incubation periods measured in months and years. Even after symptoms appear, the diseases progress relatively slowly, and several weeks or months may intervene before death occurs. Recovery is rare.

At present, there is no definite evidence of human disease caused by these latent, or chronic, viral infections. Our knowledge of the causative agents thus far stems chiefly from studies of animal illnesses that have economic significance, particularly for sheep farmers.

One of these illnesses is scrapie, a chronic disease that causes sheep, because of intense itching, to rub themselves against trees or fences. The animals weaken, lose weight, and almost invariably die. The cause of scrapie remained unknown until recently, but investigators have now established that this affliction is caused by a filterable agent, which can be used to produce the disease experimentally in sheep, goats, mice, and hamsters.

Another chronic disease caused by a filterable agent or virus is the Aleutian disease of mink, a degenerative disorder of connective tissue. Although this disease and scrapie have primary significance for veterinary medicine, we are interested in them and in other chronic viral diseases of animals—for example, visna disease of sheep and pulmonary adenomatosis—because many discoveries in human disease originated in studies on diseases of veterinary significance. We believe that the chronic viral infections of animals will provide useful models for investigations that may elucidate the causes of a whole range of human afflictions.

New smallpox drug

In the treatment of virus diseases, one of the significant medical advances in 1963 received only passing attention from the press. A relatively cheap and nontoxic chemical was found to possess prophylactic properties in preventing development of overt symptoms of smallpox in an impressive number of susceptibile persons who were exposed in an endemic area. Although it intercepted the disease, the chemical agent did not prevent the buildup of natural immunity. The compound (N-methylisatin-β-thiosemicarbazone) was first tested in 1953 and found to affect the course of vaccinia infection in mice. Trials of the drug in human subjects were carried out last year in Madras, India, where an NIAID grantee from the University of Colorado had for some years been studying the efficacy of vaccines and gamma globulin against the disease.

The results of the clinical trials showed that the drug provided almost complete protection against smallpox—3 mild cases among 1,101 treated contacts. In a control group of 1,126 untreated persons, there were 78 cases of disease, with 12 deaths. Prophylaxis was effected regardless of the vaccination status of the contacts, and the drug was much more effective than vaccination or revaccination. Side effects were minimal.

The Public Health Service has, for more than 7 years, supported this grantee's research on smallpox. The success of his work exemplifies the importance of rendering continued support on projects that represent resources for studies on major health problems.

Bolivian hemorrhagic fever

Scientists from the Middle America Research Unit (MARU) recently described the clinical features of Bolivian hemorrhagic fever. They also noted the recovery, from hamsters and mice, of a virus suspectd of being the causative agent. Hemorrhagic fever, an acute infection, has occurred in northeastrn Bolivia since 1959. Approximately 750 cases, 200 of which were fatal, were reported in the epidemic area. A similar disease, first found near Buenos Aires, Argentina, has been under study for the past 10 years. Other forms of hemorrhagic fever resembling the South American varieties have been reported in Korea, Russia, Thailand, and India.

The MARU team began its study in 1962 at the request of the Bolivian Government and with the cooperation of the Pan American Health Organization and several U.S. agencies. The investigation continued into 1963 and eventually resulted in (1) the isolation of several strains of virus from human cases, (2) clinical descriptions of a number of fever patients, and (3) extensive collections of local mammals and insects, particularly mites and ticks, suspected of being, respectively, reservoirs and vectors of the disease. The investigators analyzed case records of 51 Bolivian patients in the village of San Joaquin during a 3½-month period. When illness occurred among five members of the investigating team and contacts, additional clinical data become available. In all cases, diagnosis was confirmed by the presence of complement-fixing antibodies in the convalescent sera of the patients.

Highly preliminary findings emerging from this study indicate that a viral isolate from the spleen of a patient who died of the disease will infect both infant hamsters and mice. Laboratory studies of this virus and of other strains isolated at the same time are continuing. An enormous amount of work remains to be done. When the virus is finally characterized and compared with other agents, it may be possible to develop an immunizing antigen or vaccine. This would then have to be produced in quantity for testing in humans on a wide scale. Meanwhile, the search goes on to identify the vector of the disease and all possible reservoirs.

PARASITOLOGY

Filariasis, the helminthic infection second only to schistosomiasis as a vector-borne worm infection of global importance, is being studied in the Institute's Laboratory of Parasitic Diseases by techniques originated there. Observations of various development and growth stages of intestinal nematodes have provided new knowledge of the life cycle of the worms. Electron microscope studies, supplementing the earlier investigations, were made of worm larvae in the mosquito host.

Experimental schistosomiasis in mice was the model for studies using the antihelminthic drug Stibophen. Closely spaced injections shortened treatment time and raised worm kill from 25 to 85 percent. On the basis of these findings, preliminary trials in human patients were made, featuring continuous intravenous infusions of the drug. Results indicate the possibility of an effective cure.

Other studies have determined lethal doses of ionizing radiation to snail carriers of schistosomiasis and the effects of sublethal doses on snail growth and reproductive capacity. These findings may be applicable to the development of radiation barriers for disease control in water distribution systems. A monograph on the snail vectors of schistosomiasis in Africa, now nearing completion, will greatly aid control workers in the field.

An indirect fluorescent antibody technique has proved more sensitive than earlier tests in the diagnosis of amebiasis (dysentery caused by *Entamoeba histolytica*). *E. histolytica* and *Trichomonas vaginalis* have been successfully stored in liquid nitrogen for over 2 years, to preserve protozoan-strain characteristics otherwise lost in continuous cultivation.

A Public Law 480 project on the epidemiology of toxoplasmosis in Israel has furnished data on the occurrence of the disease there. This study has already established that there is a higher prevalance of infection in cases of eye disease (chorioretinitis) than in normal individuals. The first isolation of Toxoplasma from a patient with diseased lymph nodes was also accomplished in Israel.

Parasitological investigations are thus pressing forward against a whole front of infectious organisms. Presently available techniques should make possible the eventual clarification of host-parasite relations, serodiagnosis, immunity, and control of filariid worms. With new methods for handling amoebae and characterizing strains, NIAID scientists may be able to provide some definitive information on the pathogenesis of *E. histolytica* and related organisms, laboratory diagnosis, and treatment. It is hoped that it will also be possible to augment, extend, and accelerate our efforts against trypanosomiasis and leishmaniasis, of great importance in South America and Africa.

Malaria, which in the United States less than 30 years ago was responsible for hundreds of thousands of cases yearly and several thousand deaths, as well as economic losses in the millions, has been steadily reduced in this country. Many factors contributed to this successful campaign, among which were advances in the knowledge of the disease and its control. However, malaria is constantly being introduced by persons returning from malarious areas. In the last full reporting year (1961), for example, there was an upturn in the number of cases in this country. The potential for reestablishment of malaria in the United States is still present. Human carriers are bringing the parasites into the country. The mosquitoes which can transmit the organisms are still numerous. Parasites which are resistant to drugs could be introduced. Thus, as long as malaria is present as a major disease in many parts of the world, it remains a threat to the United States.

Research is being carried on against this parasite both here and abroad as part of the effort to eliminate malaria on a global scale. New drugs are being sought and new methods of controlling the vectors are being examined; but, generally, more effort is needed to develop and apply knowledge which can contribute to the effective control and eradication of the disease.

Malaria can serve in many ways as an example of the situation with many other infectious diseases. The gathering of information for understanding and controlling these infections must be a dynamic and progressive activity.

In 1963, scientists in NIAID's Laboratory of Parasite Chemotherapy demonstrated that *Plasmodium brasilianum*, a malaria parasite of Central and South American monkeys, could be transmitted with ease to human volunteers by the bites of infected mosquitoes. This is the first time that a New World monkey malaria has been shown to be transmissible to man by natural means.

Continuing studies of the new antimalarial CI–501, developed by Parke, Davis & Co., showed a single injection of the drug to be protective in human volunteers against a strain of *Plasmodium vivax* for a year or more, even after seven challenges (exposures to the bites of infected mosquitoes). One injection of CI–501 protected other volunteers from infection with *Plasmodium falciparum* through one to six challenges for more than a year. CI–501 also suppressed *Plasmodium cynomolgi* in monkeys for from 5 to 13 months.

At the Institute's field station in Malaya, simian malaria was transmitted to a human volunteer by an indigenous mosquito known to be susceptible to many species of monkey malaria. This finding suggests the possibility of future outbreaks of monkey malaria in man.

BACTERIOLOGY

The Institute continued to conduct and support basic research in chronic bacterial diseases, including nonviral respiratory diseases, staphylococcal infections, tuberculosis, and diseases of the urinary tract and intestines. This research, which has extended across a broad front, is designed to enhance natural resistance factors, to develop new antibiotics, and to determine promising new avenues of attack on persistent problems caused by infectious bacteria.

Institute scientists continued extensive basic studies on staphylococcal infection, which still constitute a serious public health problem. They carried on studies of the differences in physical behavior and chemical composition of cell walls of bacteria producing these infections. The goal is increased knowledge of the mechanisms involved in the biosynthesis of the cell walls of staphylococci and, consequently, greater understanding of the nature of the resistance of certain of these bacteria to penicillin and other antibiotics.

The Rocky Mountain Laboratory continued its efforts to develop an experimental tuberculosis vaccine. The success of this vaccine, which shows promise, would signalize an important advance against a chronic bacterial disease and an important cause of death in most parts of the world. The BCG vaccine now in use offers only partial protection against tuberculosis. Grant-supported research was also conducted on killed antituberculosis vaccines.

Scientists of the Institute's Laboratory of Bacterial Diseases recovered two strains of *Mycoplasma pneumoniae* previously described but lost to science for 20 years. These produce potent neurotoxins. The activity of the soluble exotoxin, which is highly toxic to the central nervous system of mice, was characterized, and some of the factors bearing on its biosynthesis were clarified. The results may lead investigators to determine that other mycoplasmas, including strains from man, produce similar substances.

In extensive extramural research in bacteriology, NIAID grantees studied the biosynthesis of bacterial cell wall components, bacterial metabolites, the mechanisms of bacterial transformation, and the persistence—despite therapy—of bacteria in tissues. Grant-supported research was conducted on the following bacterial diseases: bacterial meningitis, brucellosis, cholera, diphtheria, hemophilus influenza, infantile diarrheal disease, leprosy, listeriosis, pertussis, plague, salmonellosis, sarcoidosis, shingellosis, streptococcal infections, tubaremia, and typhoid fever. Numerous grant-supported studies were conducted in the etiology, pathogenesis, and treatment of staphylococcal infections and in urinary tract infections in infants, children, and the aged. Many NIAID grantees continued their research efforts on tuberculosis, a disease that still causes 10,000 deaths annually in the United States.

MYCOLOGY

NIAID continued its basic investigations of the role of fungi in human disease. Institute scientists continued work on histoplasmosis, a widespread pulmonary infection caused by the pathogen *Histoplasma capsulatum.* The simple method of suppressing growth of *H. capsulatum* in soil by a soil overlay was reported; it is applicable to field use in selected sites. Factors influencing germination of macroconidia of *H. capsulatum* were determined.

Advances were made in research on cryptococcosis, a worldwide, often fatal disease caused by *Cryptococcus neoformans*, a yeastlike pathogen isolated from soil and found in close association with pigeon nests and pigeon droppings under roosts. Institute scientists developed a complement-fixation technique that has proved to be an effective means of measuring *C. neoformans* polysaccharide in blood and cerebrospinal fluid of infected patients. The levels of polysaccharide offer useful diagnostic and prognostic information and are associated frequently with fatal or chronic courses of infection, despite chemotherapy.

The Institute's Laboratory of Clinical Investigations continued adding to its extensive experience with cryptococcal meningitis. In more than 40 cases, the prognosis after treatment has been studied after several years. This compendium of therapeutic information has provided a basis for programs of therapy in many parts of the United States. A continuing study of 55 patients with crytococcal meningitis has revealed factors associated with poor responses to therapy, either initial failure or replapse subsequent to initially favorable responses. Especially important unfavorable factors are the presence of other underlying diseases (for example, Hodgkin's disease), the wide dissemination of the organism (positive cultures from urine and blood), and a poorer inflamatory response in the cerebrospinal fluid (low initial cellular and protein values).

Blastomycosis is a chronic fungus infection that affects primarily the lungs of humans and several kinds of animals. Although this infection is usually mild, there is as yet no really satisfactory treatment of its more serious types. A NIAID grantee reported a significant breakthrough in the epidemiology of the disease. Until recently, a little was known about how people became infected. The grantee found the organism in soil and litter in and around old houses, barns, and chicken coops. Apparently, man becomes infected by inhaling dust from such places.

With NIAID support, an investigator spent several months at the State University, Utrecht, Netherlands, collaborating with a world-renowned expert on the polyene antimycotics. The result may be a better understanding of how an agent such as amphotericin B (a fungus-inhibiting antibiotic) destroys fungus cells and why it is also detrimental to human body cells. Collaboration of this type may assist in selecting out the antifungal fractions that are not detrimental to human cells. Such agents are needed to treat the more serious forms of disease resulting from infections such as histoplasmosis, coccidioidomycosis, and blastomycosis. Over 30 million persons in the midwestern United States have been afflicted with the first of these infections; over 10 million in the Southwestern United States, with the second; and probably several million in the Southeastern United States, with the third.

Other Institute grant-supported research was combined on the genetic mechanisms of actinomycosis, the ecology and biologically active constituents of coccidioidomycosis, the epidemiology of cryptococcosis, and the factors influencing variation in dermatophytes (the pathogenic molds that cause infections of the skin, hair, and nails). In addition, NIAID grantees in various U.S. universities conducted basic research in candidiasis, histoplasmosis, nocardiosis, and ringworm.

RICKETTSIOLOGY

The Institute's intramural work in rickettsial diseases is conducted at the Rocky Mountain Laboratory (RML), Hamilton, Mont., a world center for research in these diseases. This laboratory, whose director in July 1963 served as chairman of a special World Health Organization conference on rickettsial diseases, continued its extensive studies of Rocky Mountain spotted fever and Q-fever. The first of these diseases, which is caused by the pathogen *Rickettsia rickettsii,* occurs in the eastern and northwestern United States; the second, the infectious agent of which is *Coxiella burnetii,* has been reported in all continents. Both are still public health problems in this country.

In their work on Rocky Mountain spotted fever, RML scientists are investigating the relationship of the virulence of *Rickettsia rickettsii* strains to clinical disease in man and to the epidemiology of the disease. They are also seeking a better understanding of the natural history of Rocky Mountain spotted fever. Particular attention has been given to the ecologic factors that affect the maintenance of *R. rickettsii* in nature and to those that determine the kinds of variant strains of the organism occurring in tick populations of different localities.

Isolations of strains of *R. rickettsii* continue to be made from various wild animals, and studies of the pathogenesis of these strains are in progress. RML scientists have determined that *R. rickettsii* strains from eastern Montana possess extensive immunologic and serologic cross-reactivity with typhus rickettsiae. They isolated three of these strains from field mice.

In their investigations of Q-fever, RML investigators are adding to knowledge of the ecology of the organism, the infection in susceptible tissues and cells, the chemical nature of the rickettsial cell, and the development of improved methods of detecting and preventing the disease in man. It is hoped that these investigations can be extended to include studies of the relationship of chronic heart disease to past infection with *Coxiella burnetii.*

Research in rickettsial diseases was also conducted by NIAID grant-supported investigators at Washington State University (rickettsiae), the University of Illinois (Q-fever), and the Virginia Health Department (the ecology of Rocky Mountain spotted fever).

ALLERGY-IMMUNOLOGY

Fundamental research in immunology, conducted by the Institute and its grantees, contributed to a better understanding of allergic diseases (including those of autoallergy) and provided increased knowledge of ways to control the immune response, the major obstacle to successful transplantation of organs and tissues. This research, which also included immunologic studies of infectious diseases, is set forth in detail in the special report: "Immunologic Research Conducted and Supported by NIAID."

PROSPECTS AND PROBLEMS FOR THE FUTURE

From the highlights of principal accomplishment recited here, it will be apparent that during 1963 the continuing work of the Institute has again constituted a major contribution to world progress toward the ultimate conquest of those diseases of an allergic and infectious nature. Building on the knowledge gained in our most recent experience, work in the coming year will continue with renewed vigor and purpose toward the consolidation of past gains and the advancement of new concepts.

Although major advances have been made in the understanding and control of infectious diseases, new problem areas are continually presenting themselves. Some viruses, for example, tend to change their basic character so that vaccines produced one year may not be effective against them several years later. Drugs initially effective against bacteria, such as staphylococcus, may later lose their prophylactic value because the organism has become resistant to the drug. Compounds highly effective against malaria parasites have, in widely separated areas of the world, been counteracted by types of malaria that do not respond to the drugs. Vectors of disease, such as mosquitoes, become resistant to insecticides that once controlled them.

Adverse occurrences such as these may serve to interrupt or reverse progress achieved in the attack upon infectious diseases. In general, advances against these diseases have been far greater than the setbacks, but continued research is necessary to maintain and extend the gains that have been made.

There is need for a concentration of effort in research on arthropod-borne viruses. The large number of these viruses found in man, the variety of arthropod vectors and reservoir animals, the extensive distribution of disease caused by these viruses, and the ecological problems they present are some of the reasons why it is imperative that this research, which may have consequences of worldwide importance, be conducted. For example, the studies on hemorrhagic fever in Bolivia during the past year by investigators of the Institute's Middle America Research Unit have drawn attention to a dramatic disease of great local importance that may be closely related to hemorrhagic fevers occurring in other parts of the world.

Hepatitis, another viral infection that occurs worldwide, is still baffling research scientists. Institute virologists are working toward the time when techniques, hopefully leading to the development of a vaccine, are refined to the point where they can be used to solve the mysteries of this disease.

From the strong base in immunology derived from extensive experimental research, the Institute is now in an excellent position to extent its intramural studies of allergic manifestations to include urgently required clinical investigations emphasizing approaches to treatment. In extramural immunologic research, increased support is required to continue the progress against the manifold problems of hypersensitivity and the development and utilization of knowledge requisite in the rapidly growing area of organ transplantation.

The rising interest in the translation of basic research into instruments immediately applicable to human welfare can be expected to result in growing emphasis on Institute-directed collaborative activities concerned with the development of biological products. These activities require the coordination of intramural and extramural research and the combined resources of industry, academic institutions, and Government. Increasing and new demands will be imposed on the two collaborative programs already established. The first of these, the vaccine development program, is engaged in the difficult task of developing experimental vaccines against acute respiratory disease; the second, the virus reagents program, is striving to provide standardized reagents (antigens and antisera) required to insure reliable comparability of virus identification by laboratories throughout the world. And increased collaborative effort directed at the comparable development of standardized allergens will provide reference reagents urgently required in allergy research. In addition, studies are now being conducted on the feasibility of applying the collaborative approach to the development of vaccines and new therapeutic agents to prevent other virus and microbial diseases, including Bolivian hemorrhagic fever, hepatitis, and tuberculosis.

The 1965 request for the National Institute of Allergy and Infectious Diseases is $68,445,000. This compares with an operating level of $66,918,000 for 1964. The 1965 funds requested provide a net increase of $734,000 for research grants; $290,000 for training grants; $441,000 for direct research; $52,000 for review and approval of grants, and $10,000 for program direction. The request for 1965 is distributed among program activities as follows:

Grants and related contracts:	
Research	$38, 973, 000
Fellowships	2, 976, 000
Training	8, 239, 000
Subtotal, grants and related contracts	50, 188, 000
Direct operations:	
Research	11, 615, 000
Collaborative studies	5, 285, 000
Review and approval of grants	1, 047, 000
Administration	310, 000
Subtotal, direct operations	18, 257, 000
Total 1965 request	68, 445, 000

Dr. Andrews. Yes. I should like to present the following, Mr. Chairman and members of the committee.

During the past year, the National Institute of Allergy and Infectious Diseases carried on its broad programs of intramural, extramural, and collaborative research in the problems of infectious and allergic diseases. Advances were made in studies of viral, parasitic, bacterial, fungal, and rickettsial infections and investigations of allergy and immunology.

In viral research, our Institute scientists progressed in their studies concerning cancer-causing viruses. They investigated the extent to which viral agents are involved in neurologic and other diseases and advanced knowledge of Bolivian hemorrhagic fever.

In collaborative research, the vaccine development program carried on the efforts to produce effective vaccines against viral respiratory illnesses. The virus reagent program made available antigens and antisera related to different adenoviruses and rhinoviruses. Progress was made in the preparation of similar reagents related to several of the other respiratory viruses.

A major accomplishment in extramural research was the determination that a cheap and nontoxic drug (N-methylisatin-B-thiosemicarbazone), produced by the Welcome Co., England, provides almost complete protection against smallpox, which is otherwise almost certainly acquired by susceptible persons exposed to infection.

NIAID parasitologists demonstrated that a New World monkey malaria, Plasmodium brazilianum, is transmissible to man, determined that the experimental antimalarial drug CI–501, which we had mentioned here before, developed by Parke, Davis & Co., is effective for as long as 2 years against the most common malaria parasite, and we have carried out investigations of filariasis, schistosomiasis, and amebiasis.

Research was conducted on various bacterial, fungal, and rickettsial diseases. Studies of bacterial infections were highlighted by progress made in the efforts to develop a tuberculosis vaccine superior to the BCG vaccine now in use. NIAID investigators also continued work on promising new avenues of attack on staphylococcal infections and diseases of the urinary tract and intestines. In addition, the Institute continued to add to its unique experience with the treatment of cryptococcal meningitis and to provide informatton for programs of therapy in many parts of the Nation.

Continued research is required to maintain and extend the gains that have been made in the understanding and control of infectious and allergic diseases. Studies carried on by Institute virologists may throw light upon related problem in cancer research. Concentrated effort on research in the arthropodborne viruses may contribute to greater understanding of widely distributed diseases in which these agents are implicated.

The knowledge gained in basic research in the allergic diseases may now be applied to investigations of methods of treatment. An increased collaborative effort will provide reference reagents needed in allergy research and hopefully may result in the production of vaccines and therapeutic agents to prevent such serious diseases as Bolivian hemorrhagic fever, hepatitis, and tuberculosis.

As part of this attack on a wide array of disease problems, the Institute, by extending its efforts to train young physicians in modern techniques related to research in infectious and allergic diseases, is helping to meet the Nation's critical need for skilled professional manpower.

The 1965 request for the National Institute of Allergy and Infectious Diseases is $68,445,000, which includes $350,000 for the Gorgas Memorial Laboratory. This compares with an operating level of $66,918,000 for 1964. The 1965 funds requested provide a net increase of $734,000 for research grants; $290,000 for training grants; $441,000 for direct research; $52,000 for review and approval of grants; and $10,000 for program direction.

I will be glad to enlarge upon these if you choose.

Mr. FOGARTY. Thank you, Doctor.

RESERVE OF 1964 FUNDS

You have $66,918,000 available for 1964 and the request for 1965 is $68,445,000, an increase of $1,527,000.

Like the Dental Institute, your 1964 reserve is just a small fraction of 1 percent of the appropriation. Who made this estimate that you would obligate 99.7 percent of your funds but would not need the other 0.3 of 1 percent?

Mr. BROWN. It was made during the budget review process.

Mr. KELLY. No; I think this occurred in the apportionment process, Mr. Chairman. The amount proposed for the general research support grant program was reduced by $5 million, and there was a recomputation of indirect costs in the grants activity. The reserve of $199,000 represents this Institute's pro rata share of the general research support grant offset by adjustments necessary to cover the commissioned officers pay increase.

Mr. FOGARTY. Is the same thing all the way through all the Institutes?

Mr. KELLY. Well, a small portion of the reserves in all the Institutes, this is true of, yes, sir.

Mr. FOGARTY. You mean to tell me you can make this cost estimate in the overall appropriation that 0.3 of 1 percent would not be needed?

Mr. KELLY. This estimate was really taking the reserve on the general research support grant——

Mr. FOGARTY. Put that formula in the record, how you arrived at this 0.3 of 1 percent.

(Information requested follows:)

Pro rata share of reduction in general research support grant	$341,000
Plus recomputation of indirect costs	6,000
Subtotal	347,000
Minus commissioned officers pay increase requirements	148,000
Reserve	$199,000

RESEARCH GRANT PROGRAM

Mr. FOGARTY. You have some increases listed as program increases that turn out to be no increase in program at all. For instance, the $530,000 increase for your regular research grant program; how many additional projects will that finance?

Dr. ANDREWS. I cannot give you an exact figure of that, Mr. Chairman.

Mr. FOGARTY. If you cannot, I can.

Dr. ANDREWS. I do not think there are very many of them, I am afraid.

Mr. FOGARTY. What is that?

Dr. ANDREWS. It will not support very many, I can say.

Mr. FOGARTY. It is less than that; the answer is "Zero," according to the justifications.

This happened all the way through this budget this year. I think someone tried to show there were increases when actually there were no increases. It is leveling off. This is one of the most conservative budgets I have ever seen. Although there has been an attempt made to make it look as though we are keeping up the momentum, that is not the fact, the facts do not bear that out. I am not blaming you.

FELLOWSHIP AND TRAINING GRANTS

You are budgeting funds for 180 fellowships which is 58 less than for 1964. Are the applications from qualified students dropping off?

Dr. ANDREWS. No, sir.

Mr. FOGARTY. Is the need for professional people in this field dropping off?

Dr. ANDREWS. No, sir.

Mr. FOGARTY. For training grants, you are budgeting an increase of $290,000 and the justifications say this will allow you to make 10 more grants than during 1964. Do you really think it will?

Dr. ANDREWS. Well, of course it depends upon the size of the individual grant. It can be cut into that many, but it would be in my opinion unfortunate if it were, because it would not support very much of a program.

Mr. FOGARTY. No; I would think men like you who have spent an awful lot of time and effort in building up your institutes and are trying your best to do an effective job would get kind of disgusted when you have to put up with a budget like this.

These 10 more training grants, you are budgeting with an increase of $290,000, which I think will barely allow for increased costs, and will not allow you to make 10 more grants than during 1964. But even if it does, this is less than a 4-percent increase in funds. Will not mandatory cost increases use all of that?

Mr. BROWN. Probably.

Mr. FOGARTY. What is that?

Mr. BROWN. Yes; they probably will.

Mr. FOGARTY. This is worse than I thought it was before we really got to analyzing these budgets.

NEW VACCINES

What progress are you making in developing additional vaccines?

You refer, on page 52, to a collaborative study with AEC in this field. I did not realize that AEC was doing work in this area.

Dr. ANDREWS. In the process of making vaccines, we have made arrangements with Oak Ridge so that we are able to get the use of their large centrifugal apparatus, continuous flow centrifuge, and this permits the purification, the separation of these materials, which is essential to the purification of these vaccines.

Mr. BROWN. Concentration.

Dr. ANDREWS. Yes.

Mr. Fogarty. It was testified earlier today that some people think a virus might cause arthritis. They do not know yet. I think they gave an example of Aleutian mink that had a condition like arthritis, that was traced directly to a virus. But this is something that is new.

ROCKY MOUNTAIN LABORATORY TB VACCINE RESEARCH

Mr. Fogarty. Would you tell us a little bit about activities at the Rocky Mountain Laboratory?

Dr. Andrews. Rocky Mountain Laboratory is concerning itself largely with the new vaccine which is being developed by people at the laboratory and by people in the Montana University. They have shown that the use of tubercle bacilli, which have been suspended in oil and then exploded by decompression so that one can separate the capsule material from the contents of these organisms, has resulted in making a much more potent vaccine against tuberculosis than we have had before. You may recollect that 7 years ago, we discussed this matter. At that time we were progressing on about the same lines. We were breaking down tubercle bacilli, but they were suspended in water. All the difference which is now apparent comes from suspending these organisms in oil.

After this treatment they become much more effective from the standpoint of sensitizing these individuals.

Mr. Fogarty. What evidence do you have that this TB vaccine you spoke about is better than a BCG?

Dr. Andrews. Well, it is being compared by the individuals who made it, and I must say that the evidence thus far is not conclusive, but such as we have, it indicates that this is at least as good and quite possibly somewhat superior to the BCG.

This will have to be done on a much larger scale. These are actually small trials that we have made thus far.

Mr. Brown. In animals.

Dr. Andrews. Yes, these were in animals. So that we have got a long way to go before we are assured this is going to be a highly effective vaccine.

GORGAS MEMORIAL LABORATORY

Mr. Fogarty. There was a small increase appropriated for the Gorgas Memorial Laboratory for 1964. Are they using this to good advantage?

Dr. Adrews. Yes, sir. This laboratory, as you will recall, has now got the space and facilities to develop itself in a very large way.

It may be of interest to you to know that the man who has been director of this laboratory for the last 10 years, Dr. Carl Johnson, is leaving his administrative post, which he has occupied with distinction for this last decade, to apply himself more particularly to the field of research, which I think he likes somewhat better than administration. So he will be concerned with ecologic medical problems on the isthmus.

We have nominated for his successor, Dr. Martin D. Young, a man whom I have known for many years, in fact he was a student of ours at Hopkins when I was there. We have a great deal of assurance that he will prove to be an excellent administrator of this laboratory.

Incidentally, he was the Director of the Public Health Service Malarial Laboratory, Parasite Chemotherapy, in Columbia, S.C., for more than 20 years. In this period of time, he achieved a worldwide reputation for his researches in malaria and in certain other parasitic diseases.

Mr. FOGARTY. He sounds like a good man.

Dr. ANDREWS. I have every confidence that he will prove to be.

PROGRAM IN BOLIVIA

Mr. FOGARTY. Last year you told us about some of your work in Bolivia. What is the status of that program?

Dr. ANDREWS. This has gone steadily on. To bring you up to date, it has been possible to extract from liver exudate, material which contained a virus. We assumed, as you recall, that the agent for Bolivian hemorrhagic fever would turn out to be a virus, and in fact it has.

This virus, which has been given the name "Corvallo," after the man in whom it was found, who was sick with the disease, has been isolated, and efforts are being made to grow it in tissue culture. I think there is every probability we should be able to develop a vaccine having the virus in hand. This should help a great deal in taking care of this disease.

Mr. FOGARTY. What kind of cooperation do you get from the Bolivian Government?

Dr. ANDREWS. We have gotten excellent cooperation from the standpoint of desiring assistance in this area, but they have been unwilling thus far to supply any funds to assist in the work which has been going on there.

ASTHMA

Mr. DENTON. What have you done about asthma?

Dr. ANDREWS. We have done very little about asthma. Asthma is an allergic disease of the bronchi and lungs and other than trying to completely desensitize the people who have this unfortunate condition, there has been to my knowledge nothing else offered.

Mr. DENTON. Of course, there is a great deal of suffering from that.

Dr. ANDREWS. I am well aware of the fact; yes, sir.

I wish that we had something which could be offered. The ordinary drugs for allergy, of course, help to some degree. But they are far from being truly effective.

COMMON COLD

Mr. DENTON. What have you done about the common cold?

Dr. ANDREWS. We have been working on common cold viruses for a number of years.

Mr. DENTON. You were working on it when I was at the Institute 10 years ago.

Dr. ANDREWS. Yes, sir.

Mr. DENTON. You were working on it then.

Dr. ANDREWS. This is true, but every year seems to produce a new batch or combination of viruses. This is one of the difficulties;

the new viruses emerge from year to year. But I think that as time goes on we will develop a multivalent vaccine, a vaccine which is good against more than just one of these viral agents. I hope that this will make it easier on people who suffer with it.

Mr. DENTON. Do you have any cold vaccine at all?

Dr. ANDREWS. Yes; we have some experimental vaccines. We have not released them because they have not gone through the Division of Biologics Standards yet. But we do have some experimental cold vaccines.

Mr. DENTON. I guess 10 or 20 years ago, the doctors used to inoculate you for a cold. It was quite a common practice.

Dr. ANDREWS. Yes, sir.

Mr. DENTON. People thought it was effective. Were those cold serums any good or what were they?

Dr. ANDREWS. We do not know, of course, but from what we know of them, we rather doubt it.

There is a certain amount of relief that goes along with doing something about almost any disease. I suspect an injection of commercial cold vaccine might make somebody feel or think he felt a little bit better. But from the composition of some of these products, it is hard to understand how they could be truly effective.

What we are preparing, on the other hand, will be, I think a sound scientific approach to the matter. It will take time, and we do not want to hurry with it. It will take time not only to develop the vaccine itself, but it will have to be tested under a great many conditions before it can be released from our hands.

Mr. DENTON. Are the pharmaceutical companies doing anything about the common cold?

Mr. BROWN. Contracts are with them.

Dr. ANDREWS. They are working with us in the preparation of certain specified components for these vaccines. Some of them, of course, are making vaccines of their own which they are selling, but I am not aware of any great amount of research which is going on by the commercial houses.

GERM-FREE ANIMAL RESEARCH

Mr. DENTON. What about germ-free animal research, what are you doing in this field?

Dr. ANDREWS. The big change in germ free just occurred recently, because the man who was in charge of the germ-free laboratory was transferred to another job at NIH and the new man is primarily an immunologist. Dr. Tobie's work now is taking a slightly new slant, but the program is going ahead.

Mr. DENTON. Are you doing anything new?

Dr. ANDREWS. Yes. Dr. Tobie, who is an immunologist, has tried to utilize this opportunity in comparing the effectiveness of different immune materials in animals which have lived under germ-free circumstances in comparison with those that have not.

I do not think that he has arrived at any great conclusions about it thus far.

TRANSFER TO NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Mr. DENTON. One thing I do not understand, in your statement you say that the 1965 request for the National Institute of Allergy and Infectious Diseases is $68,445,000. Now, that checks with my records.

You say this compares with an operating level of $66,918,000. Now, my records show that you had $68,723,000 appropriated to you, almost $2 million more, last year.

Mr. MAY. The major portion of that difference was transferred to the National Institute of Child Health and Human Development.

Mr. KELLY. Transferred as part of the $34 million.

Mr. DENTON. $1.6 million?

Mr. KELLY. Yes, sir.

Mr. DENTON. That still is a couple hundred thousand off.

Mr. KELLY. Then there is $199,000 in unobligated balance reserve which makes their estimated obligations this year $67,117,000.

GORGAS MEMORIAL LABORATORY

Mr. DENTON. Now, you said something about the Gorgas Memorial Laboratory. Is that the one in Panama or the one in the zone?

Dr. ANDREWS. That is in Panama. That is the Middle America Research Unit.

Mr. DENTON. How much do you spend for that operation, Doctor? Is that the figure, $350,000?

Dr. ANDREWS. Yes, $350,000.

Mr. DENTON. As I understand it, they do research in tropical diseases.

Dr. ANDREWS. Yes.

Mr. DENTON. Yellow fever?

Dr. ANDREWS. Originally they worked in yellow fever. Of course, yellow fever has virtually disappeared in that part of the world now, though occasionally a monkey shows up with yellow fever in the jungle. But the problem of yellow fever does not exist there as it used to.

Mr. DENTON. Some years ago, I was down there and went to the Laboratory. They had had an epidemic of yellow fever. They were working on it. They were satisfied there was something besides mosquitoes that carried yellow fever, but they did not know what it was. Are you aware——

Dr. ANDREWS. I am not aware of any other vector being discovered other than the yellow fever mosquitoes.

Of course, the wild animals, which are the reservoirs of this virus—these are mainly monkeys—do extend up into Mexico and, for a while, we were very fearful that between the natural reservoir and human reservoir we would be getting yellow fever in this country. But actually this has not come to pass.

Mr. DENTON. They were very much worried about that; at that time, it was going up into Mexico.

Dr. ANDREWS. That is right.

DRUG TO PREVENT SMALLPOX

Mr. DENTON. You spoke about this new drug being discovered to prevent smallpox. Is it taken orally?

Dr. ANDREWS. Yes, sir. But I should emphasize the fact that this is not a treatment for an acute case of smallpox.

Mr. DENTON. It is a preventive?

Dr. ANDREWS. This is a preventive, which is given to people who may be exposed to smallpox.

Mr. DENTON. You already can vaccinate a person for smallpox, can you not?

Dr. ANDREWS. Yes, but it takes some time for them to acquire their protection that way; whereas, this drug——

Mr. DENTON. Say that again.

Dr. ANDREWS It will take some time for them to acquire their protection by vaccination.

Mr. DENTON. How long?

Dr. ANDREWS. Oh, probably 3 or 4 weeks. I am sort of guessing at it, but I would think it would take something of that sort.

Mr. DENTON. That long?

Dr. ANDREWS. Whereas the treatment which is being given now is something which is immediately effective.

Mr. DENTON. Well, now your Service, if a person comes in this country who is not vaccinated, will vaccinate him just at the door as you let him in?

Dr. ANDREWS. That is correct.

Mr. DENTON. They may have smallpox when they do, might they not?

Dr. ANDREWS. In this instance where we are dealing with people who are exposed to it—for example, those who are sleeping in the same room with somebody else who has smallpox—smallpox is one of the most insidious diseases we know of; it creeps into places. It is hard to understand how it does this, but it does.

If, for example, there is a room full of people sleeping with one or two cases of smallpox in it, almost all of the unvaccinated persons will, within a few weeks, come down with smallpox. On the other hand, if they take this drug the likelihood is that they would be free from it.

I am looking for the figures on the success of this drug, which I thought was very remarkable.

Mr. DENTON. You can put that in the record if you would rather.

Dr. ANDREWS. I will be very glad to.

(Information requested follows:)

In a controlled study at Madras, India, conducted by Dr. Henry Kempe, of the University of Colorado Medical Center, working under an NIAID grant, 3 mild cases of smallpox developed in 1,101 contacts treated with the drug. In the control group of 1,126 untreated contacts 78 cases of smallpox developed, 12 of which were fatal.

Mr. DENTON. Now, you find many people inoculated for smallpox, and it does not take. They are inoculated again, and it does not take. What does that signify?

Dr. ANDREWS. That signifies they are still protected by the previous smallpox vaccination or that the vaccine used was no good.

Mr. DENTON. They told me that if you went to Hong Kong, you had to have a vaccination that would take.

Dr. ANDREWS. Well, I think that it is always desirable, if you are going to a place where smallpox is prevalent, to get a new vaccination.

VACCINATION AGAINST TB

Mr. Denton. You spoke about this new vaccination against tuberculosis. Just how effective is that?

Dr. Andrews. We cannot give you a good answer to that yet, because it has not been tried on a large enough basis.

Mr. Brown. It has not been tried on humans.

Dr. Andrews. It has not been tried on humans. All the work thus far has been done in experimental animals.

Mr. Denton. What do you think about BCG? Is that effective?

Dr. Andrews. Yes. This is a good standby vaccine. You acquire protection from that because this is made from an organism which has subservient relationships and provides brief protection against smallpox. But it is not——

Mr. Denton. You mean against tuberculosis?

Dr. Andrews. Yes. I mean against tuberculosis. But it is not by any means as effective as the vaccine which is being developed, in my opinion.

Mr. Denton. Do you think you could wipe out tuberculosis with that vaccine the way we wiped out smallpox and malaria?

Dr. Andrews. Well, I think this would be theoretically possible. In actual fact it is pretty hard, as you know, to get the last few cases of any of these diseases.

PROGRAM IN BOLIVIA

Mr. Denton. Talking about this Bolivian program, you said they would not make any contribution to it. Now, this program is for their benefit in large part. Why would they not contribute any funds under the circumstances?

Dr. Andrews. They made a token contribution. I have forgotten exactly how much it was; it was not very much.

Mr. Brown. They contribute manpower.

Dr. Andrews. Yes. They did contribute manpower, they contributed buildings, facilities, things of that kind; but they did not make any very considerable money donation to it.

VIRUS-CANCER RESEARCH

Mr. Denton. What are you doing in research on viruses as the possible cause of cancer?

Dr. Andrews. We have had some considerable interest in viruses which appear to cause cancer. This, thus far, is in animals.

There have been no occasions where the viruses which cause these cancers in lower animals cause them in man.

Mr. Denton. You say there has been no occasion? No proof?

Dr. Andrews. That is true. But it is a very interesting situation, because these cancers in animals are free from demonstrable virus within a very short period of time.

I should make it clear that our interest in this subject is shared with the National Cancer Institute, because it is as much concerned as we are in the viruses which cause them. We now know that it is possible to identify some of these cancers serologically, and that others can be identified by their nucleic acids that are in the cells of these cancers.

We think that between the two, the serologic methods and the work with the nucleic acids, that it may be possible to identify cancers which are involved and conceivably then to immunize against the viruses which cause the cancers.

Mr. Denton. Do you find antibodies there?

Dr. Andrews. We have not found antibodies yet, but this would be a normal expectation and I think we will.

Mr. Denton. Now, you say that these viruses do not last long. Do you mean they do not cause cancer in animals?

Dr. Andrews. They cause them and then seem to disappear.

Mr. Denton. The virus causes the cancer and then it disappears? Is that it?

Dr. Andrews. Yes. We cannot find the virus any more. This is true.

Mr. Denton. I see. The virus causes the cancer, but by the time the cancer comes along, the virus has disappeared.

Dr. Andrews. The virus has disappeared. And the efforts which have been made to get it again have not been at all successful.

Mr. Denton. How are you going to find the virus if the cancer has not formed yet?

Dr. Andrews. Well, by serologic means which can be observed while the cancer is developing.

Mr. Denton. What do you mean by that, "serologic"?

Dr. Andrews. By testing the antibodies, by searching for the antibodies in the blood sera, which will be in the cancer, with various different serologic materials.

Mr. Denton. I thought you did not find any antibodies.

Dr. Andrews. Well, we do not immediately. But later antibodies make their appearance.

Mr. Denton. After the virus is gone?

Dr. Andrews. Yes. After the virus has disappeared, the antibodies or the antigens——

Mr. Denton. I thought antibodies were what killed the virus.

Dr. Andrews. Well, the antibodies—I am getting sadly mixed up here, I am sorry to say—the antibodies remain for a considerable period of time and it is possible, by utilizing what is known as the antibodies plus what is known about the nucleic acids of these cancerous cells to ascertain the particular new growth which is involved there.

Mr. Denton. Is there anything else you want to put before the committee?

MALARIA

Dr. Andrews. I would like to say a word or two about malaria, which is an old standby of mine.

As you know, malaria has been considered to be eradicated in this country since some time in the early 1950's, but of course it gets reintroduced each year. It comes back into the country with soldiers who are returning from malarious areas overseas and with other people who are going from one part of the world to the other. So someone has to see to it each year that malaria does not start spreading in this country. This is the responsibility of the Communicable Disease Center and the State and local health organizations of the country.

Last year, 110 persons came in with malaria. I suppose that similar situations will maintain until worldwide malaria eradication is achieved, if it ever is.

We have also found this year, as I think I mentioned, that monkey malaria in the Far East was found to be transmissible to man. This disturbed us a little because if we were going to eradicate malaria from any large area and there was a lower animal reservoir of malaria in it, this would, of course, make it much more difficult.

Now, we find that there is an exchange of malaria organisms in the New World as well as the Far East, as we now have a simian malaria parasite transmissible to man in the northern part of South America.

SCHISTOSOMIASIS

Another disease, a parasitic disease of considerable importance, is schistosomiasis. This is perhaps next in importance to malaria, as an international health problem. This occurs in many tropical areas of the world and extends into some Temperate Zone areas as well.

The parasites which cause this disease are carried by snails.

Fortunately, there is an effective medication which can reduce the worm burden of the unfortunate people who have this disease, and we are operating now with Public Law 480 funds in Egypt at a place near Rosetta—the Rosetta stone, you may recall, is one of the old landmarks.

Mr. Denton. Yes.

Dr. Andrews. And this medication is going on every day. Five thousand people are said to show up daily for treatment. It has become almost a regimented affair to handle that many people, and to give them treatment.

I remember, however, many years ago when I was in Egypt that the same sort of thing was going on. If you could get 1,000 people to come to one large tent, they would be given medication against this disease.

Mr. Denton. Do you want to ask any questions, Mr. Lesinski?

Mr. Lesinski. May I ask Dr. Andrews one question?

DIET IN RELATION TO FUNGUS INFECTION

Have you studied the possibility of diet in relation to fungus infection?

Dr. Andrews. We have not made any efforts in that direction; no, sir.

Mr. Lesinski. I had quite a heavy infection of the feet, athlete's foot, a fungus you call it, and I went on a citrus diet and it cured it.

Dr. Andrews. Really?

Mr. Lesinski. I do not know whether I became immune to it or what, but I have not had any trouble since.

Dr. Andrews. What type of diet?

Mr. Lesinski. Fresh grapefruit juice.

Dr. Andrews. I see.

Mr. Lesinski. So you have made no research along that line?

Dr. Andrews. No. We have not concerned ourselves, I think, with skin diseases of any sort, particularly.

Mr. LESINSKI. Although I do get it around my fingers in the spring and in the warm part of the year I get it on my fingers. What would be the cause of that?

Dr. ANDREWS. I have also forgotten the name of that; it is prickly heat, is it not?

Mr. LESINSKI. Call it what you want, it comes and goes.

Dr. ANDREWS. Yes. I presume that is what it is. This is also a fungal disease. This is a fungus which infects the skin and makes these little pimply places.

Mr. FOGARTY. Is there anything else you want to say, Dr. Andrews?

ORGAN TRANSPLANTATION

Dr. ANDREWS. I wondered if you would not be interested in some of the recent work that has been done in organ transplantation.

Mr. FOGARTY. I did not know your Institute did research on that. Yes; I would.

Dr. ANDREWS. The reason we have an interest in it is that the failures in tissue grafting of this kind are due to the immunologic rejection of foreign tissues by the host animal. But surgeons all over the country are developing great interest in this sort of thing. There are four very large centers—one in Denver, one in New York, one in Minnesota, and one in Massachusetts, I believe.

Mr. LESINSKI. Boston?

Dr. ANDREWS. Yes; the Peter Bent Brigham Hospital.

The great hazards, of course, in whole organ transplantation is the almost inevitable rejection of the tissue unless enough immunosuppressive drugs can be taken to reduce the rejection reaction so that this will not occur.

As a matter of fact, the National Research Council had a conference in Washington last year at which the records of all the organ transplantations that had been made up until 1955 were reviewed. This was a total of 244. Of these, most all of these transplantations had been made——

Mr. FOGARTY. Are you talking about humans now?

Dr. ANDREWS. Yes; talking about human organ transplantations, human tissue transplantation. Of 120 patients who had had transplants from living, unrelated donors or from cadavers, only 1 had survived transplantation for longer than a year.

Mr. FOGARTY. What sort of transplant was it?

Dr. ANDREWS. Kidney transplant.

Mr. FOGARTY. Kidney?

Dr. ANDREWS. Yes, sir. Of 91 other patients receiving kidney transplants from mothers or fathers or siblings, or other blood relatives, there are now only 5 alive after 1 year. No patient who received a kidney from a mother has yet lived longer than 2 years.

Then people tried to assemble groups of twins, because if you can get identical twins, presumably there should be no rejection of tissue one from the other because they have identically the same genetic history. But of the 33 sets of twins, of which 28 sets were identical—enzygotic twins—7 of these 28 who received transplants are now dead. Dr. Murray refers to this as the most shattering fact of all, because by everything that we know, these mates, one twin would give tissue for the other, and this should have worked very, very well. But, as a matter of fact, as I say, it did not.

In addition to transplantation of tissues from one human individual to the other, there have been some efforts made with what are called heterotransplantations. These are transplantations of organs from lower animals to man. There have been two recent instances in which, in the first case, both kidneys, the aorta and the vena cava, which are the large blood vessels going up and down the trunk, were removed from a rhesus monkey, a relatively small monkey, and these were installed, so to speak, within the individuals who had a nonfunctional kidney. These grafts had to be removed after 10 days because of complications, and the first patient lived only 12 days after it was removed.

Then a second case was a 43-year-old male who had had hypertensive disease and chronic glomerular nephritis. This individual received the entire complex of kidneys, ureters, aorta, and vena cava of a 41-pound male chimpanzee, and was given, of course, immunosuppressive medication and antibiotics. The antibiotic treatments are necessary because when the immunity mechanism is reduced by drugs or radiation, the patients become peculiarly susceptible to infectious disease. They have to live under virtual isolation. Any small infection, like a cold, could be fatal to them. Immunosuppressive medication and antibiotics were given to this individual, but the patient died of pneumonia 2 months after the operation.

Mr. Fogarty. Have you tried any of these transplants on germ-free animals?

Dr. Andrews. I am not aware of any.

Mr. Fogarty. Was some work not being done with dogs a few years ago?

Dr. Andrews. Yes. And the Russian scientists are working at this pretty successfully now.

I happened to see a picture recently of a two-headed dog in one of the Russian periodicals. This second head was a head that could be retracted and moved around, and apparently was a perfectly good head.

Mr. Lesinski. Mr. Chairman, at that point, this recent transplant of an arm in South America—the surgeon was assisted by a doctor from Boston. It was in the papers a couple of days ago. Do you know anything about that?

Dr. Andrews. Yes, sir. I read the case report of that.

In extremities, in limbs which have been cut or torn off, it may be possible to reattach the amputated segment. This is primarily a question of good surgery.

The question of tissue rejection, if an arm is being attached which came from this same individual, should raise no problem of rejection.

Mr. Lesinski. This was a foreign arm; a sailor, I believe, had his arm cut off and another person died, and they cut the other person's arm off and put it on the sailor.

Dr. Andrews. I do not know about this instance. I would think that the chances are that it would ultimately be rejected. But I do not know, of course.

Mr. Lesinski. I assume that from what you are saying.

Is there any way—not neutralizing, but what is the proper terminology? Of equalizing the structure of the two bodies?

Dr. ANDREWS. Not in the sense that the tissues would become mutually acceptable. I do not think that this could be done except by using immunosuppressive drugs which, under these circumstances, might at least create a union which would last for a brief period. But I doubt very much if it would last indefinitely.

Mr. LESINSKI. Getting back, as I said before, though, if you lose an ear or a nose, after a couple of hours, you can put it back on.

Dr. ANDREWS. This would be quite possible.

Mr. LESINSKI. That is all I have, Mr. Chairman.

Mr. FOGARTY. What would you like to do in 1965 that you are not doing in 1964 on this?

Dr. ANDREWS. Well, you mean on the organ transplantation?

Mr. FOGARTY. Yes.

Dr. ANDREWS. We are going to continue in assisting the support of these four groups. I think it is very important to maintain this research.

These are pretty expensive projects, the grants for these run between $150,000 to $200,000 or more a year. Much of this money, of course, goes into the exquisitely precise surgery which is necessary.

Mr. FOGARTY. All right, thank you very much, Doctor.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

WITNESSES

DR. RICHARD MASLAND, DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ECKART WIPF, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

ROBERT L. SITHENS, BUDGET OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

B. J. SADESKY, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTES OF HEALTH

LELAND B. MAY, HEAD, BUDGET MANAGEMENT SECTION, NATIONAL INSTITUTES OF HEALTH

DR. DAVID E. PRICE, DEPUTY SURGEON GENERAL

Object classification

[In thousands of dollars]

		1963 actual	1964 estimate	1965 estimate
11	Personnel compensation:			
	Permanent positions	3,798	4,676	4,837
	Positions other than permanent	183	182	187
	Other personnel compensation	87	140	122
	Total personnel compensation	4,068	4,998	5,146
12	Personnel benefits	370	455	465
21	Travel and transportation of persons	310	336	336
22	Transportation of things	58	52	52
23	Rent, communications, and utilities	154	135	135
24	Printing and reproduction	45	22	22
25	Other services	1,306	2,232	2,117
	Payment to National Institutes of Health management fund	4,680	5,075	5,276
26	Supplies and materials	660	669	685
31	Equipment	408	528	542
32	Lands and structures	8		
41	Grants, subsidies, and contributions	58,697	68,446	73,666
	Subtotal	70,764	82,948	88,442
	Deduct quarters and subsistence charges	5	14	14
	Total obligations	70,759	82,934	88,428

Personnel summary

	1963 actual	1964 estimate	1965 estimate
Total number of permanent positions	657	717	725
Full-time equivalent of other positions	41	36	37
Average number of all employees	625	690	697
Employees in permanent positions, end of year	610	706	714
Employees in other positions, end of year	88	89	89
Average GS grade	6.5	6.9	7.0
Average GS salary	$6,324	$6,991	$7,001

Program and financing

[In thousands of dollars]

	1963 actual	1964 estimate	1965 estimate
Program by activities:			
1. Grants:			
(*a*) Research	45,688	52,104	56,955
(*b*) Fellowships	1,657	1,960	1,960
(*c*) Training	11,351	14,382	14,751
Total, grants	58,696	68,446	73,666
2. Direct operations:			
(*a*) Research	6,620	7,252	7,549
(*b*) Collaborative studies	3,707	5,146	5,056
(*c*) Training activities	48	65	65
(*d*) Review and approval of grants	1,399	1,651	1,710
(*e*) Program direction	349	374	382
Total, direct operations	12,123	14,488	14,762
Total program costs, funded [1]	70,819	82,934	88,428
Change in selected resources [2]	−60		
Total obligations	70,759	82,934	88,428
Financing:			
Comparative transfers to other accounts	4,071		
Unobligated balance lapsing	8,642	1,509	
New obligational authority	83,472	84,443	88,428
New obligational authority:			
Appropriation	83,506	87,675	88,428
Transferred to—			
"Operating expenses, Public Buildings Service," General Services Administration (76 Stat. 728)	−34		
"Salaries and expenses, Office of the Surgeon General" (42 U.S.C. 226)		−28	
"National Institute of Child Health and Human Development" (76 Stat. 1072–1074)		−3,204	
Appropriation (adjusted)	83,472	84,443	88,428

[1] Includes capital outlay as follows: 1963, $329,000; 1964, $528,000; 1965, $542,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1962, $1,353,000; (1963 adjustments, −$2,000), 1963, $1,291,000; 1964, $1,291,000; 1965, $1,291,000.

GENERAL STATEMENT

Mr. FOGARTY. Dr. Masland, we shall place your prepared statement in the record and you may summarize it.

(The statement referred to follows:)

Mr. Chairman and members of the committee, it is a pleasure to appear before this committee to review with you the research and training developments of the past year directed toward understanding the human brain and preventing and curing neurological and sensory disorders.

The human brain is one of the most intricate mechanisms known to man—it comprises literally billions of individual cells, each serving a unique yet complex correlative and integrative function. A precise knowledge of this structure and its functions is essential to understanding all human activity as well as for the prevention and cure of neurological and sensory diseases. This knowledge is of utmost importance to the Nation in order that the intelligence and neurological integrity of its citizens may be preserved. The human spirit frequently can transcend the effects of physical disability, but when the brain is devastated by injury or disease, even the stoutest courage is inadequate to surmount the consequences.

In the 12 years of its existence, this Institute has developed a broad program of basic and applied research. It has undergirded this program by the training of scientists competent to cope with the complexities of this subject. Now it is selecting certain specific research targets for a concerted attack, using collaborative programs and interdisciplinary program projects as mechanisms for providing a focus on these defined areas of need.

The shortage of trained research physicians and bioscientists continues to handicap this highly specialized field. The effectiveness of those who are available, however, could be greatly increased by other areas of science and technology. For example, to understand the actual brain deficit of Parkinsonism, cerebral palsy, or mental retardation, accurate information regarding the location and function of the injured brain cells is essential. In some investigations, not only must the defect be located with accuracy but the billions of cells must also be counted. To do this for one brain, at the present time, is almost the work of a lifetime without special equipment. Instruments are now being developed to make this analysis in the space of hours or days.

Other refined instrumentation and techniques are making it increasingly possible for scientists to investigate deeper and more minute structures of bodily function than ever before. For example, through computers myriad and complex messages conducted over the networks of the nervous system are being analyzed. Such analyses are essential steps toward modification of normal functioning systems. Instruments, such as the electron microscope, reach down almost to the molecular level to provide new understanding of structural and biochemical mysteries. Parallel microchemical techniques might be developed to search for the specific enzyme defects within these structures. These defects may underlie such diseases as epilepsy, Parkinsonism, and amyotrophic lateral sclerosis, and the blinding retinal degenerations.

As contacts are broadened between scientists and technologists, the Institute is beginning to create the environment for an understanding and interchange of technological needs and capabilities. Increasingly, this scientist-technologist relationship is being formalized through various working committees. As the needs are understood, more sophisticated instrumentation for biomedical research is being developed under contract.

Since 1961, 21 specialized neurological and sensory centers for research have been activated to attack unsolved problems which have proven too complex to yield to traditional research approaches. These program projects are supporting outstanding multidisciplinary research teams. These centers include three, relating to cerebrovascular research; two, epilepsy; five, clinical neurological research; four, basic neurological sciences: and six, neurosensory centers focusing on disorders of vision, hearing, equilibrium, and speech. The newest program project is a study center for research on Parkinson's disease and allied disorders.

PARKINSONISM

The last few years have seen important advances in the understanding of basic mechanisms in Parkinsonism. The rigidity and involuntary movement characteristic of this disorder can be attributed to imbalance between the alpha and gamma motor systems of the brain. Modification of this imbalance by drugs or surgery provides some symptomatic relief. There is continuing refinement of the surgical techniques. The characterization of certain specific chemical compounds involved in the activity of these two systems suggests the possibility that a specific enzyme defect may be involved in some forms of the disorder. The Institute's program is training and supporting neurochemists to search for this defect.

Certain forms of Parkinsonism are thought to be a sequel of viral infection. Scientists at the Institute's new laboratory at Patuxent will search for such chronic viruses.

To provide a multidisciplinary approach for studying Parkinsonism, the Institute is supporting a new Parkinson's study center at Columbia University. This center is to conduct a comprehensive research program directed toward determining the cause, improving diagnostic techniques, and developing methods of treatment and management of Parkinsonism and related movement disorders. A medical information facility, integrated with this Parkinson's center, is under contract to provide for the collection and dissemination of scientific information regarding Parkinson's disease and closely related diseases and for the continuing review of this important segment of the Institute's research program.

INFECTIOUS DISEASES OF THE NERVOUS SYSTEM

Recent research studies suggest a possible relationship between latent viruses and certain neurological disorders, such as Parkinsonism, multiple sclerosis, and amyotrophic lateral sclerosis. To further this study, the Institute last year initiated a program in collaboration with the Patuxent Wildlife Research

Center and this year established a small field station in New Guinea in cooperation with the Australian Government.

In New Guinea, research scientists are particularly interested in the increasing information showing similarities between kuru, a neurological disorder affecting the Fore natives in the eastern highlands of New Guinea, and scrapie, a disease affecting sheep and goats and believed caused by a latent, slowly developing virus. At the Patuxent Center, material from patients with a variety of chronic neurological disorders is being inoculated into animals for prolonged observation. As facilities become available, demyelinating diseases which have been found in deer, moose, and raccoon will be studied in an attempt to find the virus, bacteria, fungus, or biochemical agent causing the disorders. Pathological studies of central nervous system disease in this wildlife have shown a picture similar to pathological studies of Parkinsonism and multiple sclerosis in humans. This is expected to be useful in research studies since multiple sclerosis has not been found in animals, and it has not been possible to reproduce the disease in animals experimentally.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

A renewed emphasis has been placed on ALS research this past year at the Institute's Bethesda laboratories, its research center on Guam, and through grant-supported research at various medical centers across the Nation. Usually appearing after the age of 30, this paralytic disorder relentlessly attacks the long nerve tracts of the brain and almost invariably terminates in death in a few years.

Since ALS is 100 times as common on Guam as it is in the continental United States, an intensive search has been instituted on Guam to seek any genetic or environmental factors which may be responsible. The Institute's research center on Guam has established a registry of 2,500 patients and relatives and is investigating every aspect of the environment, including modes of living, diet, occupational contacts, and infections. At post mortem examination, the brains are subjected to electron microscopic examination and brain cells are cultured for a possible virus.

Of particular immediate concern is recent evidence suggesting that the incidence of ALS is high not only among the native Chamorro population but also among other residents. It is therefore planned to survey all non-Chamorros age 35 and over who have resided on Guam for 5 or more years. At the same time, an effort will be made in collaboration with the followup agency of the National Research Council to determine whether ALS is especially prevalent in veterans who were assigned to the Western Pacific islands during World War II.

Scientists at the Institute's Bethesda laboratories have found that the clinical picture of ALS may possibly be a manifestation of several different disease entities. Cases have been found in association with collagen disease, gout, diabetes, and hidden cancer. Also, research at Bethesda has resulted in the discovery of a very slowly progressive type of ALS occurring in young adult females. Research on this disorder will be further emphasized at the Clinical Center during the coming year.

MULTIPLE SCLEROSIS

Multiple sclerosis continues to be a critical, unsolved problem of modern medicine. The Institute's program has confirmed the existence of a unique geographical distribution of the disorder. It is rare in tropical climates, but may occur in young individuals moving to a cold climate, or in people moving to a warm climate, even at periods of several years after leaving the cold region.

Although multiple sclerosis has not been duplicated exactly in animals, the pathological processes of experimentally produced allergic encephalomyelitis bear many resemblances to the disease. The Institute's program has concentrated heavily upon determining the nature of the autoimmune mechanism underlying this experimentally produced disease in tissue culture. Transitory blocking of this autoimmune reaction has been accomplished by X-ray, desensitization, vitamin deficiencies, and chemical agents, but the practicability of such measures in the human disease is dubious.

In addition to the laboratory at Patuxent where a search is being made for chronic virus infections possibly associated with the disorder, preliminary negotiations are underway to establish an Institute-supported multiple sclerosis disease study center. The amount of interest and progress in this area is pointed up by plans of the New York Academy of Sciences to hold a symposium on "Research in Demyelinating Diseases" early in 1964.

NEUROMUSCULAR DISEASES

The Institute's program over the last few years has demonstrated that the group of conditions ordinarily spoken of as "muscular distrophy" is, in fact, a number of closely related but distinct disease entities. A broad program is underway to differentiate these conditions through meticulous microscopic examination of muscle tissue and the biochemical analysis of muscle and of body fluids. The detection of essential structural or chemical defects underlying these diseases is also under study. At least three newly defined syndromes have been distinguished through this program, the most recent being an unusual condition characterized by flaccidity of the muscles, mental retardation, and obesity. It is believed that an undisclosed metabolic disorder may underlie this newly discovered entity.

Although no treatment capable of arresting musclar dystrophy has been discovered, a variety of treatment for some of the symptoms of muscle diseases has evolved. A new drug, valium, is helpful in controlling certain involuntary movements observed in dystonia and spasticity; dilantin can reduce the annoying muscle contractions of amyotrophic lateral sclerosis; emivan, combined with prostigimine, can relieve respiratory distress in ALS patients; biochemical controls of ionic balance, important to the transmission of nerve impulses, are useful in certain forms of periodic paralysis; and ACTH may relieve the painful conditions of certain inflammatory diseases such as dermatomyositis.

EVALUATION OF THERAPY

In 1960, the Institute sponsored a conference on Evaluation of Therapy at which the outstanding leaders of clinical investigation in neurosensory disorders met to consider the needs in the therapy of various disorders and the methodology required to assure a program of safe and reliable drug evaluation. It became evident that accurate classification of diseases, and rigid criteria to measure improvement were essential for such a program, and were not available for many neurosensory disorders. Task forces, organized at this meeting, have been evolving methodologies. The panel on multiple sclerosis has developed a set of criteria for evaluating new therapies for symptoms of this disorder. The headache panel has published a classification of headache types and is using this in the testing of new compounds for relief or prevention of headache. The epilepsy panel has developed and pretested a new methodology and is now starting an evaluation and comparison of two commonly used drugs.

For more than 20 years adrenal cortical extracts have been used in treating myasthenia gravis patients. This year, a study was conducted by clinical investigators in six hospitals to test the effectiveness of ACTH on myasthenia gravis patients. Forty-three patients were selected whose signs and symptoms were limited to the muscles around the eye. There was no evidence that ACTH produced improvement in the patients studied.

In addition to this broad program, the Institute's cooperative study of cerebral aneurysms is providing critical data regarding the value of four different forms of therapy for his highly fatal form of stroke.

Within the collaborative perinatal project, an extensive program for the determination of the effects of drugs, taken by the mother, on the human fetus has been developed.

In order to assist the Institute in the planning and evaluation of these developing programs, an NINDB Advisory Panel on Evaluation of Clinical Therapy was established this year. Through this Panel, outstanding leaders of the field will provide a continuing review of this important segment of the Institute's activities.

STROKES

Cerebrovascular disease, or stroke, stands third as the cause of death in the United States, and is the leading factor of chronic disability. In addition, many persons have "small strokes" that are unknown at the time, but which lead to subtle impairment of intellectual capacity.

In order to attack this large problem, a Joint Council Subcommittee on Cerebrovasucular Disease was established by the Heart and Neurology Institutes in 1961. Composed of Advisory Council members from both Institutes and other consultants having particular interest and experience in cerebrovascular research, the Subcommttee is reviewing research progress, identifying research and training needs, and recommending new program developments. Currently it is concentrating its efforts on cerebrovascular blood flow and epidemiological studies of cerebrovascular disease.

The Fourth Princeton Conference on Cerebrovascular Disease, sponsored by the American Neurological Association and the American Heart Association, and supported by a grant from the Institute, will consider research progress during the past 3 years including advances in the study of atherosclerosis, fibrinolysis, anticoagulants, and cerebral blood flow as well as various diagnostic techniques.

Recognizing the inadequacy of criteria concerning the treatment of intracranial hemorrhages, the Institute appointed an ad hoc committee a number of years ago to consider the problem. Later, a Cooperative Study of Intracranial Aneurysms and Acute Subarachnoid Hemorrhage was established, with a central registry at the State University of Iowa. During the first phase of the study from 1957 to 1962, the necessary research protocol was developed, and the four most promising treatments for cerebrovascular aneurysms were identified. The second phase of the study, now underway, is concerned with differentiating when, or under what conditions, each of these four therapies is most applicable. Twenty-one cooperating laboratories (including one in Great Britain) are submitting their data to the central registry, where it is being pooled and analyzed. The study gives promise of providing more adequate criteria to the medical community concerning the treatment of this medical emergency.

INTERNATIONAL RESEARCH

The international research program of the Institute has been limited to outstanding projects utilizing scientific skills, materials, or populations not readily available in the United States. An important aspect of this program is the "paired" grants enabling medical institutions in this country to work cooperatively on specific research projects with leading research centers abroad. Of particular interest are three paired grants relating to glaucoma, hearing loss, and blood groups.

Investigators at the State University of Iowa are coordinating their glaucoma studies with those of an outstanding team in Sweden. The paired grant makes it possible to profit from the Swedish team's advanced knowledge of the pharmacology and biochemistry of glaucoma. It also takes advantage of an inexpensive, convenient supply of monkey eyes in Sweden.

A paired grant to study hearing loss has been established with the Johns Hopkins University and the Christian Medical College Hospital at Velore, India. In India, where many people have nutritional and infectious diseases, it is possible to accumulate a sizable number of cases more readily and less expensively than in the United States. It is also possible to study the effectiveness of drug therapy for the control of such disorders. Moreover, the pathological specimens, temporal bones and brains, needed for the study are easier to obtain in India. These pathological specimens and other information will be sent to the Johns Hopkins University for analysis and recording.

In another area of cooperative international research, a team of American and European investigators has launched a unified attack on brain damage including mental retardation by attempting to determine the possible relationship between human chromosome patterns and blood groups in patients with neurological and related diseases. Through this study, investigators from the United States, Sweden, the Netherlands, France, Italy, and England are exchanging research personnel, specimens, and information on newly developed methodologies and results. Through their joint effort, they hope to obtain a faster answer to an important question: Can tests of blood groups signal an error in human chromosomes undetected by present methods? If so, this finding will have particular value for patients with neurological disorders, including mental retardation.

HEARING AND SPEECH

One of the most rapidly growing segments of the Institute's programs relates to disorders of hearing and speech. Surveys to obtain reliable knowledge of the prevalence and severity of hearing and speech impairments, currently being pursued, are essential to the design of effective research programs.

It is estimated that between 1½ and 2 percent of all school-age children suffer from severe hearing loss. In a pilot study of hearing problems among school-age children supported by the Institute at the University of Pittsburgh, it was revealed that possibly as many as 10 to 15 percent of these children suffer from potentially dangerous ear disorders. In as many as 5 percent, active ear disease presented an actual threat to hearing.

Important advances have occurred in differential diagnosis of disorders of hearing and communication. The Institute is supporting a series of conferences concerned with establishing a unified nomenclature and classification of communication disorders. Standard classification is an essential step toward obtaining reliable incidence and prevalence data but is more important for the establishment of programs for the development and evaluation of therapy.

Considerable uncertaintly still exists regarding the myriad causes of loss of hearing. Among children, perinatal factors including hereditary conditions, asphyxia, neonatal jaundice, infections, and toxic effects of drugs are of major concern. Among the other age groups must be added the effects of additional toxic agents, nutritional defects, endocrine disorders, allergies, tumor, and injury from accident or noise.

Accurate differentiation of the causative agents may be extremely difficult during life. Microscopic examination of the ear following death may provide clues regarding the causative agent, but only if there is accurate information in the patient's previous history. For this reason, the establishment of the national temporal bone program is of extreme importance. The Institute now has established a number of centers to collect temporal bones for hearing research. Individuals suffering from hearing loss may will their temporal bones to such centers. Pathological investigations have already clarified our knowledge of conditions such as otosclerosis. Some conditions of hearing thought to be associated with irreparable injury of the nerve are actually the result of the extension of the otosclerosis process from the middle ear into the very depths of the ear's structure. This new knowledge is leading to improved surgical procedures for the relief of this frequent cause of hearing loss in middle age.

NEUROSURGERY

The improvement of neurosurgical techniques has increased the number of conditions amenable to surgery. Among those currently treated by neurosurgery are tumors of the brain and spinal cord; cerebral aneurysms and other circulatory disorders of the brain; spinal cord compression resulting from diseases of the bony spine, such as herniated intervertebral discs and arthritis; disorders resulting from injury to the brain and spinal cord, including epilepsy; abnormal or involuntary movement diseases, such as Parkinsonism, hydrocephalus and other congenital anomalies; and a group of miscellaneous conditions including intractable pain.

The neurosurgeon needs to find ways to stop blood circulation of the brain for extended periods of time to permit reconstructive work on the blood vessels not now possible. Recent research providing important information toward this objective relates to studies on body temperature and atmospheric temperature changes.

Low temeprature or hypothermia tends to arrest circulation, but it also produces changes which alter the effects of many drugs. The brain at low temperatures is more susceptible to antibiotics, anesthetics, and muscle-relaxant agents. Many of these phenomena are being explored for possible therapeutic value in infection and tumors. On the other hand, some drugs, unable to pass through the blood-brain barrier at normal tempertures, may permeate the brain at low temperatures and cause permanent damage.

The use of high pressure or hyperbaric surgical techniques for brain surgery is being studied. It is hoped that the brain can be saturated with sufficient oxygen to allow circulation to be arrested. However, oxygen poisoning remains a problem.

The blood supply to the brain under anesthesia has been studied with particular reference to the anesthetic agent fluothane. This drug reduces blood pressure but permits an adequate blood flow to the brain during major surgery. The effects of other chemical and physical agents are being investigated, among them radiowave energy, as potential producers of safe, light surgical sleep.

Recent advances are aiding stereotaxic surgery, used most often in the treatment of Parkinson's disease. Here the tip of an instrument must be located within a certain region of the brain. A new technique, which might be called electronic navigation, is being developed to make this locating procedure more precise and, at the same time, minimize the amount of brain tissue destroyed to secure the desired surgical result. This technique utilizes the characteristic electrical responses of various portions of the brain as reflected through the oscilloscope or a loudspeaker.

Research regarding brain swelling or edema is underway at laboratories throughout the world. Any injured tissue swells, but in the case of the brain, the problem is more serious because the brain is incased in the flexible skull. Studies show that fluids leave the blood vessels of the injured brain and lie in the cells and spaces causing widespread damage far beyond the zone of original injury from a blow, gunshot wound, hemorrhage, or tumor. Function may be impaired and life endangered or lost as a result of this swelling. Increased knowledge about this phenomenon may lead to improved care of injured patients as well as those who have undergone brain surgery.

NEURORADIOLOGY

New techniques in neuroradiology have been developed at the Institute's Bethesda laboratories this past year. These techniques will aid in the localization of brain tumors and other abnormalities of the brain.

A new technique of axial transverse encephalography was originated and new equipment developed to obtain X-ray pictures of the brain in a new dimension. This technique has made it possible to locate certain tumors and other abnormalities which previously escaped detection.

A new and painless radioisotope technique for safe and clearer delineation of brain deformities has been developed to study fluid-filled spaces in the brain. By using radio-iodinated human serum albumin (RISA) injected into these spaces, this technique shows the flow and currents of cerebrospinal fluid, giving greater insight into the normal flow and its derangements which occur after injury, and with tumors, bleedings, infections, and such conditions as hydrocephalus and brain cysts. A new atlas of brain abnormalities, shown with this technique, has been prepared to guide scientists working in neurology, neurosurgery, and related scientists working in areas concerned with mental retardation.

ACCIDENT AND INJURY

It is estimated that the Nation spends more than a billion dollars annually for medical fees and hospital expenses as a result of various types of accidents. This is an area of primary concern to the Institute because brain, spinal cord, and peripheral nerve injuries present some of the most difficult problems for medical science to solve.

The most common single cause of hospitalization of children is accident and injury, a large percentage of which are from injuries of the head and brain. Many of the serious permanent residuals of head injury, including mental retardation, appear to develop progressively during a postconcussion reactive phase. Prompt and effective management of these cases could materially reduce the severity of permanent neurological damage.

In addition to progress previously reported in the regeneration of severed peripheral nerves, this year an Institute grantee has taken a major step forward by transplanting a human nerve segment, sometimes as long as 5 inches, and succeeding in restoring nerve function. The method has proved successful even when surgery is performed as long as 3 years after the original injury. The grafts, which are frozen irradiated nerves from recently deceased donors, are shielded by a thin porous plastic sheath to enhance growth. Radiation used in sterilizing the graft modifies it and makes it possible for the recipient to accept the graft without an inflammatory tissue reaction.

Using specially designed physiological apparatus at Institute laboratories, it is now possible to measure accurately the rate of peripheral nerve regeneration, analyze the factors influencing the rate of regeneration, and perform studies on drugs suspected of enhancing or inhibiting the protein synthetic activity of the neuron.

Regeneration of the spinal cord has been possible under certain favorable conditions, but successful function in man has not been achieved. In lower animals, functional recovery is commonplace. Comparisons of mammalian and amphibian regeneration are seeking an explanation for the limitation of regeneration in the higher forms.

EPILEPSY

Research is adding gradually to an understanding of the causes of epilepsy and is providing improved means of controlling the attacks. Prevention of seizures, of course, is the ultimate goal.

In the basic sciences, research is centered on the brain cells within which must reside the actual trigger mechanism of seizures. By thrusting a microelectrode into the individual nerve cell, one can observe the action within a neuron when a seizure occurs. Intraneuronal microelectrode techniques show promise of answering many basic questions concerning excitation and inhibition. Electron microscopic studies also are adding to our understanding of the minute structures of the brain.

The use of drugs continues to be the primary treatment for epilepsy. The development of drugs capable of controlling some of the less responsive types of epilepsy is still being pursued. Because the testing of the effectiveness of drugs leaves much to be desired, an organized program for the evaluation of drug therapy is of utmost importance. Progress in this program has developed more rapidly since many artificial methods of producing epilepsy in animals have been found. These include the application of drugs and chemicals like metrazol, alumina cream, penicillin, or cobalt; the undercutting of the cortex to produce hypersensitive neurons; local freezing; and the use of loud noises to produce seizures in certain strains of animals.

A collaborative study relating to epilepsy is now in operation as part of the Institute's program for the evaluation of therapy. The efficacy of old and new drugs is being tested. The way drug action may be modified by changes within the body from temperature, hydration, and hormones is evolving from pharmacological studies and is expected to yield better control of drug therapy.

One type of epilepsy that has received much too little attention is infantile myoclonic seizures. In some instances, early treatment with steroids can prevent lifelong blighting effects, but there is a great need to understand the cause, pathology, and biochemistry of this disorder to develop more effective therapeutic and preventive measures. The research attack on infantile myoclonic seizures will contribute significantly to the problems of mental retardation since this type of seizure, occurring in the first 3 or 4 years of life, is often associated with mental retardation.

COLLABORATIVE PERINATAL PROJECT

Central to the Institute's attack on nervous system damage during the period surrounding birth is the multi-institutional collaborative project studying 50,000 mothers and their babies. During the past year, a preliminary analysis of project information has been made in pursuit of factors of pregnancy assumed to be related to neurological and sensory disorders and to perinatal mortality. as well as prematurity and congenital malformations.

Preliminary analyses are focused upon such factors as toxemia, age and height of the mother, prior pregnancy history, induction and duration of labor, forceps delivery, breech presentation and delivery, and cesarean section.

These pregnancy studies demonstrate that with both the young and older mothers there is a substantially increased risk regarding perinatal mortality, prematurity, and congenital malformations. It has been demonstrated that women, whose last prior pregnancy ended in a live-born child weighing less than 4.4 pounds, have a prematurity rate of 36 percent in the subsequent pregnancy. Conversely, if the last prior child weighed in excess of 7½ pounds, the prematurity rate in this pregnancy drops to around 3½ percent.

The study of the placenta has revealed many interesting findings which appear to be related to abnormal pregnancy outcome. Thus, defective development of the umbilical artery, called aplasia, was reexamined with project data confirming that this condition occurs frequently in association with other congenital anomalies and is related to an increase in perinatal mortality.

Inflammation of various placental tissues is a relatively frequent event and its association with prolonged labor, fetal and neonatal deaths, and its almost complete absence in elective cesarean section, seem to suggest that infection may be the crucial factor. In addition, a gross disparity between placental and birth weights identifies groups of children with a high perinatal mortality rate. This is particularly apparent when the placental weight is disproportionately small for a given birth weight or length of pregnancy.

Many studies are seeking to identify characteristics of newborn children which may forecast an increase in neonatal mortality rate or neurological abnormality rate in surviving children. To date, the neurological test known as the Apgar rating, both at 1 and 5 minutes after birth, appears by far to be the best predictor. The 5-minute Apgar rating seems to be much more strongly associated with neonatal mortality and neurological morbidity at the 1-year level than the 1-minute Apgar rating.

A marked increase in neurological abnormalities has been observed in premature children. Although only 10 percent of all births are premature, 30 percent of neurologically abnormal children at 1 year of age are prematures. About 10 percent of all neurologically abnormal children at 1 year show signs of asphyxia in the immediate neonatal period. With project data, the importance of asphyxia-like states can be evaluated.

An extensive reinvestigation of the problem of hyperbilirubinemia of prematurity and its importance in brain damage is now in progress. Investigators are questioning the standards currently being applied in bilirubin testing and are suggesting that lower levels of danger should be established.

In an extensive investigation of perinatal infections, 36 percent of 25,000 pregnant women showed evidence of prior infection with toxoplasmosis, and 2½ percent indicated recent infection. Seventeen percent were found susceptible to German measles. Over 10 percent experience some viral infection during pregnancy.

To evaluate the effects of drugs during pregnancy, data from project pregnancies are available and are being supplemented by data from other sources. These and many other individual analyses are now making contributions to our knowledge of the many perinatal factors in the neurological and sensory disorders of infancy and childhood.

In research related to the project, investigators at the Institute's Laboratory of Perinatal Physiology in San Juan, P.R., studying the harmful factors which produce injury to the newborn, have found that infant monkeys asphyxiated and resuscitated at birth develop varying degrees of symptoms comparable to cerebral palsy, epilepsy, deafness, and mental retardation.

A colony of more than 900 rhesus monkeys makes up the total population of this perinatal physiology center, probably the most extensive center for such investigation in the world. Of these 900 monkeys, approximately 450 free-ranging monkeys are on the island of Cayo Santiago; some 150 monkeys, free-ranging and in compounds, recently have been added to the islands of Isla Cueva and Isla Guayacan; and a colony of some 350 caged animals is located at the University of Puerto Rico's School of Medicine, with adjacent laboratory facilities.

In the past year, further investigations of the harmful factors which produce injury of the newborn and methods of countering these deleterious effects have continued. Evidence has accumulated in recent years that certain changes in the blood caused by oxygen deprivation could be minimized and damage lessened through the use of intravenous injections of glucose and alkali. These further research studies confirm the value of this treatment, which could have important implications in preventing certain forms of cerebral palsy and mental retardation.

For the future, it is planned that this project will continue to evolve as one facet of the Institute's broad program to investigate the nature and mechanism of action of perinatal factors in cerebral palsy, mental retardation, and other neurosensory disorders of infancy and childhood.

Further elaboration of the protocol for the main study is still in progress, paralleling the age of the offspring. Major emphasis this year will center upon refinement of the examination of these children at age 5 for the purpose of detecting and characterizing evidences of brain damage through psychological testing. The examination schedule for the 6- to 7-year followup, which requires a definitive neurosensory examination, is now being developed for pretesting. A protocol is also being developed to provide for the followup through age 12 of at least a selected subsample, including those with evidences of cerebral palsy, mental retardation, blindness, and deafness in order to observe the further growth changes in this group.

During the current year, analysis is, of necessity, largely confined to data from the neonatal phases of the followup. Major attention is centered upon the mechanisms of action in insufficiency of placental circulation, and failure of respiratory gas exchange in the newborn period, which are among the major causes of asphyxial damage of the nervous system.

The search for infections causing injury of the nervous system in fetal and neonatal life will be intensified. Specific efforts to produce cerebral palsy, deafness, blindness, or mental retardation in monkeys by infection with rubella virus are in progress. The role of toxoplasmosis is a cause of epilepsy, mental retardation, and blindness in infancy is also being reevaluated. These studies involve serology, virus isolation, and experimental animal infection techniques.

The intake of patients according to the present protocol should be completed during calendar year 1965. From the analysis of the data now in hand two types of projects are being formulated which will be needed for the solution of unresolved problems.

For some studies, additional numbers of patients with neurological or sensory disorders will be required. These may be obtained by retrospective studies, by the followup of high risk pregnancies, or by the use of a specialized type of protocol. Such investigations, for example, may be utilized for the study of women in the older age groups, and for problems of diabetes and toxemia. Toxemia is by far the most common obstetrical complication, accounting for a high fetal loss and affecting about 10 percent of the project population

For other problems, specifically focused studies are being developed. For example, current data analysis suggests that brain damage and even cerebral palsy are resulting from a much lower blood bilirubin level than previously believed. The study data, however, fail to distinguish with certainty the effects of neonatal jaundice from other concomitant deleterious factors. A controlled trial of exchange transfusion may be required to resolve this issue.

For these diverse investigations, the Institute's Perinatal Research Branch will continue to provide central staff resources and data processing.

In 1964 expenditures by grants to the collaborating institutions will be approximately $7.4 million; in 1965, expenditures will be approximately $7.65 million. In fiscal year 1964, the budget for central staff resources and data processing is $2.8 million, which includes an increase of $600,000 over fiscal year 1963. It is anticipated that this level of operation will continue in 1965.

DISORDERS OF VISION

The Nation's blind now number nearly 400,000; many more have such serious vision problems that they are unable to hold regular jobs or lead normal lives, and an estimated 3,500,000 people in the United States have some visual impairment.

Until recently, the vast task of providing adequate medical care for these people with eye disorders had absorbed the supply of trained manpower in this vital field. As a result, eye research had been a relatively neglected field.

However, beginning in 1952, the Institute has supported the training of approximately 750 teacher-investigators in ophthalmology. This training effort has contributed to the 50-percent increase in ophthalmologist-per-population ratio (2.2 per 100,000 to 3.3 per 100,000), and an increasing number of these highly trained men and women have been accepting full-time academic and research positions.

The effect of this additional scientific manpower is also evidenced by recent advances in the understanding and treatment of blinding disorders. Glaucoma, an eye condition which is latent in about 2 percent of the population over age 40, can now be diagnosed with precision, and improved treatment makes it possible to save vision in cases diagnosed early. This year, studies on the response of glaucoma patients to steroid therapy has provided an even more sensitive diagnostic tool and has thrown new light on the genetic aspects of this condition.

Therapeutic procedures for many eye disorders are being improved. Surgical procedures for cataract and retinal detachment are being refined. Infections of the eye, including toxoplasmosis and certain other diseases, are yielding to antimicrobial drugs. One new agent, cystosine arabinoside, appears more effective than IDU (5-iodo-2-deoxyuridine), discovered 2 years ago by an Institute grantee, in treating virus infections of the cornea .

In addition, laboratory research, which has no immediate clinical application, is adding to our understanding of the anatomy and function of the various parts of the eye in health and disease. These basic studies form the foundation for new cures and means of prevention for the blinding disorders that yearly claim the sight of thousands.

TRAINING

The essential task of building a pool of scientific manpower to fill the many vacant positions for teachers and investigators in the neurological and sensory areas has been of primary concern to the Institute. Since an estimated 10 million persons suffer from neurological disorders, it is rather startling to learn that of the approximate 275,000 physicians available in the United States, only about 1,000 are neurologists, or 1 neurologist for every 10,000 persons with neurological disease.

This drastilc shortage of well-trained neurological scientists clearly demonstrates why the Institute has given top priority to the development of new training programs, the expansion of existing programs, and the recruitment of able young physicians to prepare for careers in the neurological sciences. Since there are not enough trained personnel to staff this expanded training effort, the Institute has given emphasis to the preparation of professional personnel for careers in academic medicine at the same time that it continues to support the training of future investigators.

Despite the Institute's concentrated efforts in training, the total number of physicians in full-time clinical research and teaching is still relatively small. However, there has been sufficient time to measure some of the impact of the Institute's training programs. In the last 2 years, for example, the total number of physicians in full-time research or teaching in the neurological and sensory areas has approximately doubled: In neurology, the number in full-time research or teaching has increased from 139 to 287; in neurosurgery, from 58 to 113; in ophthalmalogy, from 64 to 128; and in otolaryngology, from 33 to 77. Important advances also have been made in the training of individuals in the preclinical disciplines basic to the study of neurological and sensory disorders. Special emphasis is being given to training activities in neurochemistry, sensory physiology, epidemiology, and neuropathology.

The Institute will continue its efforts to encourage physicians and scientists to receive training in the neurological and sensory areas. It will also continue to see that facilities are available to provide for the highest order of training, and to insure that the individuals trained are prepared for careers in research and community service.

CONCLUSION

With an increased number of well-qualified investigators now available, progress in neurological and sensory research is proceeding more rapidly on all fronts. Nevertheless, the unsolved problems are still extensive. Because of the Institute's mandate to arrive at solutions to neurological and sensory disease problems with all possible speed, many institutions and many scientific disciplines are now cooperating in the conquest of these handicapping and sometimes fatal disorders. This added impetus to the research effort hopefully will advance the day of successful prevention, treatment, and cure of many neurological and sensory disorders.

The request for 1965, Mr. Chairman, is $88,428,000 which provides for increases in grants as well as increases in direct operations. It is distributed among program activities as follows:

Grants:	
Research	$56, 955, 000
Fellowships	1, 960, 000
Training	14, 751, 000
Subtotal, grants	73, 666, 000
Direct operations:	
Research	7, 549, 000
Collaborative studies	5, 056, 000
Training activities	65, 000
Review and approval of grants	1, 710, 000
Administration	382, 000
Subtotal, direct operations	14, 762, 000
Total, 1965 appropriation request	88, 428, 000

Mr. Fogarty. Go right ahead, Doctor.

Dr. Masland. Mr. Chairman, members of the committee, the Institute is developing a number of multidisciplinary centers for research in the prevention and cure of the major disorders of the brain and sensory systems. This year, the number of such research centers has increased from 15 to 21. One of the most recent centers is the one for Parkinson's disease and allied disorders of involuntary movement. This study center is an important Institute program development, since it embodies not only a comprehensive program of research, but also will serve as a focal point for the review and dissemination of Parkinson's information to other investigators and to the medical community.

Advances of science underscore the opportunity and needs for highly precise instrumentation to further biomedical research in the complex mechanisms of the human nervous system. Progress has been made toward increasing the interaction of neurology and technology, so necessary if medical scientists are to have the full assistance of modern methodology. The development of instrumentation for those handicapped by neurosensory disorders, as well as the advance of basic knowledge of the nervous and sensory systems, will require an organized effort to insure the necessary collaboration.

New knowledge of prematurity, neonatal jaundice, and asphyxia is being derived from the early analysis of the wealth of data now available within the Institute's multi-institutional collaborative perinatal project. As children studied in the project increase in age, the analyses will be extended to consider the relationships of these factors to the occurrence of neurological disorders, and to problems of vision, language, and hearing.

Related animal studies with some 900 monkeys at the Institute's Laboratory of Perinatal Physiology in Puerto Rico also have supplied valuable information on events and circumstances that occur during the perinatal period affecting pregnancy outcome. The Laboratory's research focus on asphyxia has been helpful in indicating means of lessening brain injury caused by lack of oxygen.

In conclusion, Mr. Chairman, the request for the National Institute of Neurological Diseases and Blindness for 1965 is $88,428,000 as compared with the $82,934,000 available in 1964. These funds will provide program increases of $4,851,000 in research grants, $369,000 in training grants, $69,000 in direct research, and $20,000 in review and approval of grants, in addition to certain built-in costs, such as pay increases and full-year cost of positions new in 1964.

Mr. Fogarty. Thank you, Doctor.

The amount available for 1964 is $82,934,000 and the request for 1965 is $88,428,000, an increase of $5,494,000.

Dr. Masland. Yes, sir.

RESERVE

Mr. Fogarty. What is the reason for your reserve of $1,509,000?

Dr. Masland. At the time these estimates were prepared, in the fall of 1963, it appeared that the funds could be left unprogramed subject to release if the need arose.

Mr. Fogarty. I see. Well, that is about the same in all of the institutes.

Dr. Masland. Same.

PROJECT GRANTS

Mr. FOGARTY. Most of your increase is for the regular research grant program, an increase of $4,256,000, but you are worse off, it looks like to me, than any of the other institutes. Your table on page 78 shows you have to cut back the number of new projects you will be able to finance, from 302 to 240. That is a cut of 62.

Dr. MASLAND. Yes, sir.

Mr. FOGARTY. Is that right? It is hard for me to believe those figures.

I think you have one of the most important institutes in the whole group. Maybe that is why you are the last one to appear; because this is the worst I have seen so far. I did not think you could get much worse than the others we have had, but this is a terrible situation.

Are you receiving fewer approvable applications?

Dr. MASLAND. No, sir. We have had a steady increase in the number of applications each year.

Mr. FOGARTY. Is there a decreasing need for research?

Dr. MASLAND. No, sir.

FELLOWSHIPS

Mr. FOGARTY. For fellowships, you show no increase in funds, but show an increase of three in the number you will finance.

Dr. MASLAND. Yes, sir.

Mr. FOGARTY. With increased costs, it is going the other way with most fellowship programs; the same amount finances fewer fellowships. Why are you different?

Dr. MASLAND. Well, under this budget, we would propose to finance fellowships at the lower level, which are less expensive. We could handle more that way.

Mr. FOGARTY. Oh, I see.

TRAINING GRANTS AND PERSONNEL NEEDS

Now, I have the same question about your training grants. In money, you are budgeting an increase of less than 3 percent. This surely will not even cover the increased mandatory costs. But you estimate you will make 31 additional grants. How will you be able to do this?

Dr. MASLAND. Some of those grants will actually be special traineeships, and these are relatively smaller sums. We can give a greater number of those.

Mr. FOGARTY. But your budget increase is less than 3 percent. I did not think that would cover the increased mandatory costs; will it?

Maybe your budget man could answer.

Mr. WIPF. We have a total increase of $369,000. This will enable us to support almost 31 additional grants within the mandatory cost of the program.

Mr. FOGARTY. It takes care of all the mandatory cost increases?

Mr. WIPF. It will take care of the mandatory costs in the training program we are supporting and the 31 grants associated with this mandatory cost.

Mr. FOGARTY. Do you have an estimate of what increased costs will be for 1965?

Dr. MASLAND. Suppose we put this in the record.

Mr. FOGARTY. Yes. Right at this point.

(Information requested follows:)

The mandatory increased cost for training grants is $1,109,000 in fiscal year 1965; however, this is offset by decreases in new programs and other nonmandatory items within this activity.

SHORTAGE OF TRAINED PERSONNEL

Mr. FOGARTY. Tell us how serious the shortage of trained people is in this field.

Dr. MASLAND. First I would like to say, Mr. Chairman, that the training program has, in fact, developed very well. It has been a highly productive undertaking. There has been an impressive strengthening of the manpower situation, largely as a result of the training program.

For example, over the last 5 years, the total number of people in training, including those that we are supporting in neurology and in ophthalmology, has increased 30 percent; in otolaryngology, 25 percent; in neurosurgery, it is 75 percent. These are very significant increases.

Mr. FOGARTY. When you start from almost zero, any increase is significant percentagewise.

I am thinking about mental retardation. Everywhere I go people say that we do not have the trained personnel, they just are not available. We cannot hire them.

Dr. MASLAND. That is true.

Mr. FOGARTY. That is what I get in my State and everywhere I go. They are not available. We have the money, but we cannot hire them.

Dr. MASLAND. That is right. There are very good signs that this is being broadly recognized across the country. The demands for fellowships to our Institute have markedly increased. We have had many more than we had anticipated. I think this is a reflection of an increasing awareness of the importance of the neurological sciences.

Also in the past 2 years, the number of people in full-time teaching and research positions has doubled. Of course, this is starting from a very small figure.

Now, the productivity of this program is further evidenced by the fact that, although the people coming out are still very young men—after all, they are young programs—these men are rapidly moving into positions of leadership. One of our men, Dr. Kaufman of whom I will speak later has made a very important discovery in the treatment of blinding diseases. He is a man who has just recently come off our training line.

I reviewed the list of participants in three important international conferences that were held here this year, one on multiple sclerosis, one on Parkinsonism, and one in glaucoma. Between 10 and 20 percent of the participants were people who had completed our training programs.

Mr. FOGARTY. Is that so?

Dr. MASLAND. At a recent meeting developed by the Armed Forces Institute of Pathology on pathology of blindness, a group of top-level lecturers were invited to give a very senior course, and 5 out of the 10 lecturers were former trainees of the Institute. So I think we have good, solid evidence of the productivity of this program.

Mr. FOGARTY. As far as you have gone, you have. But you have a long, long way to go.

Dr. MASLAND. Yes; there are two areas which are seriously unmet.

Mr. FOGARTY. What are they?

Dr. MASLAND. There is the problem of the management of individuals in the institutions for the mentally retarded. Here are large numbers of neurologically damaged children, and you know far better than I that these institutions are almost completely unstaffed by people who are experts in the nervous system.

NEUROLOGICAL PATIENTS IN STATE MENTAL HOSPITALS

The other is the problem of the neurological patients in the State neuropsychiatric hospitals—these are the State institutions which handle mental patients. But in most of those institutions, there is a very large group of patients who are suffering from neurological disorders and they are really the forgotten people.

Mr. FOGARTY. Why has not something been done about this?

Dr. MASLAND. Again, it is to some extent a problem of manpower shortage, but we are——

Mr. FOGARTY. Will this Mental Health Act help in that area?

Dr. MASLAND. To some extent.

Mr. FOGARTY. And grants to State hospitals?

Dr. MASLAND. To some extent it may, but there needs to be a greater focus on the problem of the individual with neurological disease.

Mr. FOGARTY. What do you think the States ought to do?

Dr. MASLAND. I think much can be done by the establishment of units for neurological patients in association with the general hospital. There is isolation of patients in the large State hospitals very——

Mr. FOGARTY. Can you give us something more on this for the record?

Dr. MASLAND. Yes. I could prepare someting for the record on this.

(The information requested follows:)

PATIENTS WITH NEUROLOGICAL DISORDERS IN STATE AND GENERAL HOSPITALS

Studies of populations of patients within the State psychiatric institutions have revealed unexpectedly large numbers of individuals within these institutions who were actually suffering from neurological disorders. One report found "a considerable variety of neurological disorders, comprising 20.9 percent of the population," and concluded that "the largest group of 'organic' cases in large psychiatric institutions is composed of cerebrovascular disorders and primary cerebral degenerations; and that pharmacologic control of convulsive disorders (epilepsy) is the most important neurologic therapeutic problem."

A report from the Camarillo State Hospital, California, shows in detail the prevalence of neurological disorders in the resident population of that institution as of April 30, 1962. (Within this report, patients with senile arterioosclerotic and alcoholic disorders are not classified as neurological unless there are positive neurologic signs.) The overall prevalence of neurological disorders in the Camarillo population was 19.1 percent. Among these patients, 27.2 percent suffered from epilepsy; 23.6 percent syphilis of the central nervous system; 10.8 percent from the results of head injury; and 8.2 percent from circulatory disorders. Included in the total were cerebral palcy, Friedreichs ataxia and related disorders, postencephalitic disorders, multiple sclerosis, Parkinson's disease, and various forms of chorea and athetosis.

Statistics report that of 124,416 admissions to public prolonged-care hospitals in 1958, 41,961 suffered from "chronic brain syndromes" due to such organic brain diseases as syphilis, chronic alcoholism, drug or poison intoxication, arteriosclerosis, epilepsy, and senile brain disease.

In analyzing the individual statistics and case reports, one finds that the underlying problem in most of these conditions is cerebrovascular disease. With the progressive increase in the aging population, this situation can be expected to deteriorate further.

Dr. MASLAND. I know of one survey, for example, of a State hospital in California, 20 percent of the patients were individuals who were there primarily because of crippling neurological disorders.

Mr. FOGARTY. Like what?

Dr. MASLAND. Multiple sclerosis, Parkinson's disease, strokes.

The other large group are those with arteriosclerosis and with dementia secondary to cerebrovascular disease. This is another large area in which we are attempting to develop a more effective research program.

Mr. FOGARTY. Perhaps you have brought this problem to the attention of the committee before, but if you have, I have forgotten about it.

Dr. MASLAND. It has been largely overlooked.

PROGRAM FOR STROKE PATIENTS

Mr. FOGARTY. Yes. What are you doing in the area of strokes. Would you put a statement in the record?

Dr. MASLAND. I will prepare something for the record on this.

Mr. FOGARTY. All right.

(Information requested follows:)

A PROGRAM FOR STROKE PATIENTS

Strokes are a symptom of neurological damage resulting from interruption of the circulation of the brain by leakage of blood from a vessel (cerebral hemorrhage), by plugging of a vessel (embolus) or by clotting of blood within a narrowed or damaged blood vessel (thrombosis).

One ordinarily thinks of a stroke as a severe, dramatic episode. Less well recognized, but equally important is the "little stroke" or the "silent stroke." In this condition, the occlusion of a small blood vessel leads to a minor less evident impairment of brain function. Repeated episodes of this sort, often unrecognized, lead eventually to gross impairment of physical and intellectual capabilities—a true dementia. Because of a lack of adequately equipped and staffed community resources for research, detection, and treatment of stroke patients, many must be cared for within our large psychiatric hospitals, which are presently ill equipped for a comprehensive program of research and therapy in this area. The "organic dementias" now represent 20 percent of the population of such institutions.

Usually the stroke occurs upon a background of prexisting disease of the cerebral blood vessels, and predisposition to strokes might be recognized by special examination. An adequate national program should thus provide for a coordinated program of research and service for three stages of the disorder, namely: (1) early detection and prevention; (2) immediate treatment of strokes; and (3) management and retraining of the neurologically damaged stroke patient.

The central resource of a national program needed to meet this problem is a network of regional stroke centers. Each of these centers, staffed by an outstanding research team, must be equipped with the most modern diagnostic instruments, should provide inpatient and outpatient treatment services and include a rehabilitation program with an inpatient nursing unit to make possible long-term therapy for the restoration of the lost neurological functions.

Within this environment, clinical research and improved patient care will both advance together, each facet of the closely integrated program lending support to the other.

These centers can be developed as a natural evolution, starting from the three cerebrovascular research centers now being supported by the NINDB. To this end, the presently existing research activity would be strengthened by an extension of service functions as outlined above. A number of additional regional stroke centers could be established, having at the outset, varying components of the total integrated research and service elements ultimately required, if funds for personnel and construction were available.

Such large regional centers, serving as focal points for research, program development, and training, can provide but a fraction of the Nation's needs. As in the case of mental illness, every community must have coordinated resources for the stroke patient. All too often, the general hospital provides but limited services to meet the long-term needs of the neurologically disabled. The isolated environment of the large neuropsychiatric institution, or of the nursing home, does not lend itself to the active program these patients deserve. It is desirable, therefore, that new hospital construction include special provision for inpatient and outpatient care of the neurologically disabled. Construction of beds for such patients in large isolated institutions should be discouraged, and these resources should be used for the development of needed resources within the community hospital complex.

As a part of this total effort, certainly every medical school should have a visible focal point for research, patient care, and teaching on strokes. A modest beginning would be the establishment, within the NINDB, of a grant program for "Stroke Stations" comparable with the "Heart Station" which has served such a useful function within the hospital and medical school complex.

Essential to the development of this program is the training of skilled research and clinical personnel to man it. The refinement of diagnostic methodology, on the one hand, and the development of more effective anticoagulant therapy on the other, are both placing a new standard of performance on the physician. To meet this challenge, the NINDB and the NHI are developing a training program to prepare neurologists and internists to conduct investigations in this important area. A broad program of physician education would be an important extension of this activity. The regional stroke centers are in a position to provide a natural environment for such a program.

NEUROLOGICAL PATIENTS IN STATE MENTAL HOSPITALS

Mr. Fogarty. What can we do about this other problem you brought up?

Dr. Masland. I think it is a matter of working with the universities.

Mr. Fogarty. Working with the universities?

Dr. Masland. Tying it in with the universities. Because of the manpower problem.

Mr. Fogarty. The hospital and the university, you mean?

Dr. Masland. Yes. Finding those institutions where there is a strong university group that is interested.

We have something of this sort in Minnesota. There we have a cerebrovascular study at the University of Minnesota. The man in charge of this project is also studying the problem in the State hospitals in that area.

Mr. Fogarty. I think we are starting that a little bit in Rhode Island, are we not, between Brown University and the State hospital? And also the center for the retarded.

Dr. Masland. Yes.

Mr. Fogarty. I know they are sharing some personnel.

Dr. Masland. Yes.

Mr. Fogarty. Sharing the cost, too.

Dr. Masland. I think that is a very forward-looking program in Rhode Island as it is developing.

SHORTAGE OF NEUROLOGISTS

Mr. Fogarty. Now, your justifications say, on page 81, there is 1 neurologist for every 10,000 persons with neurological disease. I would think that would impress the people who pass on your budget. It impressed me a few years ago when you, or I think it was Dr. Bailey at that time, said there was only one, not "qualified" neurologist—what do you call them?

Dr. Masland. Certified.

Mr. Fogarty. Certified neurologist in four States in the Southwest.

Dr. Masland. Yes.

Mr. Fogarty. Only one in four States?

Dr. Masland. That is right.

Mr. Fogarty. I just could not believe that was possible. But now you say there is only 1 for every 10,000 persons with neurological disease.

What are you doing about that? What are you trying to do?

Dr. Masland. We are progressively strengthening the training program by increasing the number of programs and increasing the number of people in each program. In addition——

Mr. Fogarty. You cannot increase it much with this budget you have this year. I think you would like to, but you are not being allowed to with the money that has been allocated to you.

I interrupted you. Go ahead.

Dr. Masland. We also have "Developmental grants," which make it possible for a medical school which has no program in neurology to bring in a person to start one.

Mr. Fogarty. There has been a lack of interest in the medical schools in neurology, too, has there not, over the years?

Dr. Masland. There has been.

Mr. Fogarty. In the number of hours devoted to this area?

Dr. Masland. Yes. There has been in the past. This is also improving. There is a tremendous interest and recognition of the importance of this program.

Mr. Fogarty. That is good.

COLLABORATIVE PERINATAL PROJECT

In our report last year, we requested that more definitive recommendations be provided on future courses of action for the collaborative perinatal project and that immediate steps be taken to analyze and disseminate data already collected. What have you done in this regard? Tell us how this program is working out.

Dr. Masland. The plans which have been developed in response to this envisage two aspects. The first has to do with the continued study of the group of children who were brought into the study under the present protocol. The oldest of these children is now about 3. The youngest still is to be born. We will continue bringing cases in for another year or so until we have an adequate number.

Originally we had envisaged following these children until the age of 7. Recently we have been in conversation with staff of the Office of Education who were very much interested in this program, and we are onw making plans for the followup of some of these children through the age at least of 12. This will give us the opportunity to observe the effect of the previous condition of the child on his school performance.

The Office of Education would like to know the basis for school failure and, in our studies, we have had very accurate information on the history of the child. We have very careful evaluations of language development and of intellectual development in the preschool period. We hope to be able to use this information to predict the children who are going to have difficulty in school.

If we expect to improve the level of education of our underprivileged individuals, it is quite possible that this may have to start before they get to school. For this, it may be necessary and desirable for us to predict ahead of time the children who may have difficulty in school, in order to institute remedial procedures before they are lost in the first and second grade.

We have developed a very careful screening test to be given at the age of 3 and at the age of 4. This can be validated on the basis of the school performance of these children at a later time. This information will provide future guidance for the selection of children in need of special training before they are in school.

Mr. Fogarty. When that is done, where are we going to get the personnel to give these children that special training that they need?

Dr. Masland. This is also an area of our concern.

Mr. Fogarty. That is also a concern of the Office of Education.

Dr. Masland. That is right.

Our problem is to develop the information—the basic knowledge. We are working very closely with the Office of Education. They will have the problem of getting this knowledge and training to the teachers who are going to use it. That is going to be a very important job.

Mr. Fogarty. We may have to start a program for schoolteachers like we have for general practitioners, in mental health.

Dr. Masland. Yes.

Mr. Fogarty. Or else work it into the curriculum of the schools preparing the teachers.

Dr. Masland. Certainly it is going to be very important.

Mr. Fogarty. Especially for the teachers of the lower grades.

Dr. Masland. Yes.

Mr. Fogarty. I meant to ask Dr. Felix yesterday and did not do it, about the program for Protestant ministers, Catholic priests, and Jewish rabbis. We still have that program going in mental health?

Mr. Kelly. I think so.

Mr. Fogarty. Dr. Price?

Dr. Price. I am quite certain we do.

Mr. Fogarty. For the Jewish faith, Protestant faith, and Catholic? I think that program has worked out very well. Many people with mental problems go to their minister, priest, or rabbi. I would assume if teachers were given this sort of training in mental retardation they could recognize many of these things in time to be much more helpful than they are now. Is that a fair statement?

Dr. Masland. You are absolutely right.

Mr. Fogarty. Is there anything you want to add to it?

ANALYSIS BEFORE SCHOOL AGE

Dr. **Masland.** Yes; I would like to comment also about the importance of recognition of individuals with specific problems even prior to school age. We have had some conversations with members of the Bureau of State Services, Neurological and Sensory Disease Services Branch, on the development of screening tests for visual defect, hearing loss, and language disabilities.

For example, a child with a modest hearing loss should have that hearing loss recognized at the time he is learning to talk, at the age of 3 or 4. Some of those children should have hearing aids. If not, their language does not develop properly. There is evidence that there are specific periods of readiness during the course of development; if a person does not learn to talk at the right age, he has a lot of difficulty later on. You have to train them before they go to school.

Mr. **Fogarty.** I have seen some remarkable results from young people, especially those who have had speech defects being corrected with the proper teaching. They have a program in Rhode Island and they have done a wonderful job in correcting speech defects. If not corrected at an early age, they generally follow a person right through life.

Dr. **Masland.** That is right.

Mr. **Fogarty.** You generally do not try to do anything about it after the teens.

Dr. **Masland.** It is much more difficult later on.

PROGRESS IN HEARING AND SPEECH RESEARCH

(The following additional report on this subject was submitted at the request of the committee:)

Special Report: Hearing and Speech

PROGRESS IN HEARING AND SPEECH RESEARCH

In the past year, progress through research has been particularly hopeful in the crucial areas of prevention of deafness and of testing the hearing of the young child, in infancy, in the critical speech-developing period around 3 years, and at school age. Another area where dramatic progress continues is in the surgical restoration of hearing through one of several operations for otosclerosis. Young and middle-period adults are the usual beneficiaries of these research advances.

However, the entire field of speech and hearing continues to enlist the research efforts of scientists in both the basic and the clinical disciplines. Selected advances will be included in this report.

THE SIGNIFICANCE OF HEARING FOR SPEECH

Unless a child has sufficient hearing, by natural or artificial means, he will not develop normal speech, and must be taught by special educational methods. As scientists have become increasingly aware, much more important than the actual ability to produce physical speech (involving making sounds which convey ideas), hearing and speech are the key factors in developing the raw material with which thinking is done—the names for persons and objects, for actions, and as intelligence progresses, for ideas.

Having learned speech, the individual who loses his hearing retains the raw materials for thinking and conveying his needs and ideas—unless his loss of speech involves a loss of the functioning of the speech center within his brain. However, the baby who is born deaf or loses his hearing in infancy lacks the usual means of hearing through which he acquires facts and ideas. Consequently, he may wrongly be considered mentally retarded when all he lacks is medical attention to his hearing, as indicated, and such special education as the deaf or hard-of-hearing require if his hearing loss cannot be cured.

The mature person also has speeech production problems related to hearing. in the middle years, hearing loss is typically due to otosclerosis (overgrowth of bony tissue immobilizing the tiny bones which should provide the middle-ear conduction of sound); noise damage from industry and airplanes; and damage from accidents and from such disorders as stroke. Such hearing loss is often followed by deterioration in the quality of speech which may adversely affect job functioning and normal social life. In the elderly, hearing loss poses even graver threats to speech because important communication often drops off when the input of ideas from listening to speech diminishes.

Because of the significance of good hearing and normal speech for total health, the Institute has prepared a pamphlet, "Hearing Loss, Hope Through Research," to assist with the public education on the importance of prevention and early medical care of hearing disorders.

MAGNITUDE OF THE PROBLEM

Estimates, based on small and inadequate surveys, of the numbers of persons afflicated by hearing disorders range from a conservative 3 million, of which 125,000 are totally deaf, to more liberal assertions that 80 percent of the population of the United States has some sort of deficit in hearing in one ear or the other. Information concerning speech impairments is even more uncertain.

There are many reasons for the vast differences of conjectures in these areas. But before accurate data regarding prevalence and severity of these communicative disorders can be made available, reasonable agreement must be reached regarding classifications of the disorders, establishment of criteria, and standards for measuring impairment.

In an effort to help resolve some of the questions, the Institute supported a workshop on nomenclature of communicative disorders to evaluate a proposed impairment code for disorders of hearing, voice, speech, and language comprehension and use. The second national workshop will give further consideration to these matters when it meets early in 1964 under the sponsorship of the Institute's Communicative Disorders Research Training Committee and the rehabilitation codes. At that time four week sessions will be held: two on developmental problems, and two on problems of adult impairment. These workshops represent only intermediate steps necessary to the ultimate adoption of a uniformed system of classification throughout the scientific community concerned with hearing and speech.

In order to provide for continuous information on incidence and prevalence of hearing loss, the Institute is laying the groundwork for a national reporting network on deafness. The Institute already has encouraged active efforts to obtain more accurate information on prevalence.

In June 1963, an extensive report was published, providing an analysis of data collected on 4,078 children between 5 and 14 years of age. Gathered between June 1958 and August 1960 by grantees in Pittsburgh, this is the first report of reliable hearing-level determinations and examinations of the ears, nose, and throat of children in this crucial age. From the norms of this study, deviations due to hearing loss can be discovered and treated or the children given remedial methods of education. The study was supported by an Institute grant with several major goals, including development of efficient case-finding methods for those with hearing loss, and use of these methods to estimate the magnitude of hearing loss in schoolchildren.

A limited study over a 5-year period found that slightly more than 1 out of 10 pupils in New York City had a hearing impairment discoverable by a screening test.

In a report in 1963 of three hearing conservation programs conducted for groups aged 65 and over, in Cleveland, approximately 60 percent had some degree of hearing loss. As previously mentioned, standards are being studied for definition of degree of impairment. In comparison to the 60-percent Cleveland finding of "some degree of hearing loss," the U.S. National Health Survey reported the prevalence of "hearing impairment" of those from 65 to 74 years at 13 percent, and the 75 years and over age group at 25 percent.

Measurable hearing loss does not always interfere with daily living needs for understanding conversation and receiving warnings of danger. Its interference with occupation varies sharply with the occupation: the violinist who must create a tone of exact pitch, and the physician who must hear variations in the heart through a stethoscope obviously require more acute hearing than most individuals.

However, the sharp rise in hearing loss in persons over 65, even though the majority may be retired from active employment, indicates the need for further research in prevention and treatment for this group. Because their numbers in the American population are increasing, attention to their hearing problems will be rewarding to the American social structure.

MECHANISMS OF SPEECH AND HEARING

How we hear

There are two main theories of hearing. One proposes that the individual's ability to recognize the pitch of sound depends upon which portion of the hearing mechanism is stimulated by a given sound. A second theory proposes that pitch is recognized by the rate at which the sensitive structures of the ear are stimulated by sounds of different frequency. An understanding of the nature of the hearing process is obviously essential for a clear knowledge of its disturbances. Through actual recording of the responses of the internal ear to different types of stimuli, and through the construction of mechanical models of the ear, new information regarding these mechanisms is being developed. A clearer picture of which mechanisms may be responsible is coming into focus.

More information on the brain's regulation of hearing

An important recent discovery has been that the brain itself has the ability to regulate the sensitivity of the ear. Apparently this "feedback" mechanism alters the sensitivity of the sense organ for hearing, and thus controls the intensity and quality of the incoming signals. Through new and improved histological and histochemical techniques, the pathways for this mechanism are being accurately outlined. Study of the brains of animals subjected to asphyxia and kernicterus suggest that these pathways may frequently be damaged by these conditions. Such studies are providing new insight into the complexities of the disabilities of the hard of hearing.

The central integration of hearing

Institute-supported scientists are continuing to study the distribution of the nerve pathways through which sounds are transported from the ear through the brain stem and into the complicated network of the hemispheres of the brain.

An important investigation this year has been involved with mapping those brain areas of the cat concerned with response to sound, sight, and body sensation. The areas of the brain to which the sensations are relayed, as well as those which have secondary involvement, have been mapped out by analyzing their electrical responses. Responses have been charted as close as 1 millimeter apart.

These studies are serving to support an earlier hypothesis which states that a stimulus in any one of these three sensory categories not only activates a specific area of the brain, but also through an association mechanism activates a central association system.

Almost uniquely characteristic of the human is the typical localization of certain complex functions such as speech in the left hemisphere of the brain. The inner relationship of the two hemispheres is thus of crucial importance to an understanding of some of these complicated functions.

Institute grantees are concentrating on studies of the interrelationship between the two hemispheres, responses to contralateral and ipsilateral stimuli, and the effects of disconnection of right and left hemispheres of the brain by injury or disease. These studies have an important bearing upon the complex language disabilities observed in children and adults.

The studies in humans continue to focus on the problem of the localization of those areas of the brain associated with specific types of speech defects. In studies of aphasia, there is general agreement that the expressive difficulties are associated with the anterior portions of the brain whereas receptive difficulties are associated with more posterior portions. However, much closer localization of speech functions is still required.

Dolphin "speech" is studied

A serious handicap in the study of language has been the lack of animals capable of speech which could be subjected to experimentation. For this reason, the discovery that the dolphin appears to have the capability for highly complex auditory communication represents an important opportunity in this field. Therefore the Institute is supporting intensive investigations of the methods of communication of the bottlenose dolphin. This year Institute grantees noted that a special pair of short calls indicates physical distress and alerts nearby dolphin to aid the distressed animal. Additional studies of the dolphin brain are being carried forward in order to map the areas involved in this language function and to determine whether it can be equated with the human capability.

Memory for language is investigated

Since intellectual abilities are important to normal language development, the Institute's research program is putting special stress on understanding the process of memory in relation to speech and language facility. Studies conducted this year with intracerebral injection of an antibiotic, puromycin, have consistently caused loss of short-term memory without affecting long-term memory. In addition, these studies have indicated distinction of brain areas associated with recent and longer term memory.

Other Institute grantees this year have probed further into the electrical mechanisms, at the single nerve cell level, involved in the initial stage of memory recording. Their studies add weight to theories concerning the effects of polarization on the retention of information transmitted during the period of current flow as well as the thought that, in memory, a sequence of electrical impulses is transformed into structural changes in the nervous system.

Other investigators, including Institute scientists, have continued to explore the relationships between lesions or stimulated areas of the brain and memory deficits. Recently developed experimental techniques have made it possible for Institute grantees to investigate the retention of a memory trace localized to one hemisphere of the brain and the conditions under which the trace is transferred to the other hemisphere.

The possibility that memory may be associated with enzyme induction, with special emphasis on the effects of increased prophyrin concentration, has been subject to research during the past year. Molecular theories of memory associated with the importance of various types of molecules including DNA, RNA, proteins, and lipids have received further experimental study. There are, however, many other aspects which must be investigated to provide a comprehensive theory of the structural basis of memory.

CAUSES OF DISORDERS OF HEARING AND SPEECH

Intensified study of known or suspected causes

Among the many factors known to be associated with speech and language disorders which have been subjected to study in 1963 are prenatal effects, including maternal infectious diseases, drug ingestion, and Rh blood incompatibility between mother and child. Further factors are birth injuries including asphyxia at birth, severe infantile infections such as meningitis, genetic influences, biochemical abnormalities including metabolic disorders and nutritional deficiencies. Still others include injury, tumor, neurological diseases, emotional disturbances, and diseases of the circulation of the nervous system. The Institute has developed a broad program to elucidate the nature and mechanisms through which these harmful conditions operate.

The Institute's collaborative perinatal project, which involves the study of 50,000 mothers and their offspring from earliest pregnancy, provides a vast store of information regarding the causes of any hearing disability. Each of the offspring of these thousands of pregnancies is being subjected to careful examination when newborn, again at the age of 3 years, and at the time of school entrance.

A variety of causes are being investigated within this vase project. For example, the effects of drugs taken by the mother on her developing child is receiving increasing attention. Detailed records of drugs taken by each of these women will be available.

The effect of viruses as known or suspected causes of damage to hearing, as well as to other portions of the brain and nervous system, is also being studied. Rubella (German measles) has been known for several years to cause deafness, blindness, and mental retardation in a high percentage of babies when the mother has been subjected to this disease during the first 3 months of pregnancy.

Reports of hearing damage to the infant from shingles and mumps in the mother during pregnancy add to the suspicion that several kinds of virus infection in the mother could explain some of the deafness of the newborn.

Because these viruses are known to cause deafness, other viruses which might be comparably damaging are the subject of intensive research. Institute scientists maintain more than 100 virus antigens against which the blood of pregnant women in the cooperative study of 50,000 pregnant women can be checked.

When Institute investigators confirmed the identity of the rubella virus, its antigen was added to the previously known ones in this research project, and immediate work on a preventive vaccine for women in the childbearing age was started. The vaccine is expected to be generally available at an early date, and its use can prevent the deafness and retardation rubella has been causing.

Noise as a cause of hearing loss

The Institute is concerned with the effects of noise upon the hearing. An intensive investigation reported in 1963, supported in part by the Institute, showed that persistent hearing loss in cats increased when a given degree of loud noise was maintained for an increasingly long period. The amount of persistent hearing impairment decreased when longer intervals of quiet were allowed between periods of noise. Assuming that these results with animals are valid in humans, this finding indicates that rest periods away from loud noise should be provided for people exposed to such stress.

These observations were confirmed by actual microscopic examination of the injured cat tissues. Tissue changes varied considerably in different cats but the location of the damage appeared to be nearly common to all, indicating a specific mechanism of damage from deafening noise.

A possible cause of cleft lip or palate

This Institute has long been interested in the research attack on cleft lip and cleft palate. This condition frequently is associated with speech and language disabilities. The Institute looks forward to potential practical application of the Dental Institute's research on a possible cause of this form of congenital malformation; inadequate nutrition with vitamin B. Clinical studies produced highly encouraging results with vitamin B supplement when this was provided in the first 3 months of pregnancy to women having previously born one or more children with cleft lip or palate. Larger studies will be needed, however, to verify these results, which could lead to an important preventative measure.

Another important form of language disability is stuttering. This is a common, long-recognized, and often severe speech problem. Well-defined and precise observations of individual stuttering histories and the events before, during, and after specific episodes of current stuttering have been made.

Genetic factors leading to deafness and speech disorders

Many speech and hearing disabilities are attributable to genetic defects. The metabolic disorder, histidinemia, the first biochemical disorder known to be associated with a specific intellectual disability, is under investigation. Delay in language development is the prominent clinical disability associated with this condition, which previously has been almost indistinguishable chemcally from phenylketonuria. New chemical tests are now making it possible to distinguish histidinemia from phenylketonuria through spectophotometry. The exact effect of histidine and a method of treatment still require further study, but clinicians are actively exploring the metabolic pathways of handling histidine in the normal and abnormal individual.

Another form of genetically determined deafness is "Alport's syndrome." In this condition a family history of nephritis is accompanied by nerve deafness.

PREVENTION OF HEARING AND SPEECH DISORDERS

Early detection is crucial

The early recognition of disease of the ear, or disability of language functions, is an absolute essential in prevention. Many forms of impending deafness, if recognized early, are subject to cure.

Within the Institute's collaborative project there exists an ideal opportunity for the development and testing of methods for the early recognition of such disabilities. Early testing of infants begins in the Institute's collaborative perinatal study with a highly refined test of hearing in the newborn. It continues with specific testing of hearing at the regular interim examinations, and expands to include highly specialized language tests at the age of 3 and 7 years.

In young children, it has been essential to develop methods for testing hearing which do not rely upon the child's formal cooperation. The psychogalvanic skin resistance test relies upon conditioned reflexes of the sympathetic nervous system by which perspiration automatically indicates that a sound has been heard in the uncooperative patient or child. In other tests, electroencephalographic responses of brain waves have appeared to produce objective evidence of hearing. "Peep show tests" have been developed for children who are trained to observe attractive pictures in response to a heard sound. These methods, combined with recently developed computer techniques, provide sensitive indications of hearing.

So successful have these early tests become, that a baby of 10 months wearing a hearing aid provides visible proof that this child is receiving every known attention to hearing in order that speech may develop to its optimum degree.

In order to increase the validity of these new tests for hearing loss in the infant and young child, more research is needed for determining the normal development of hearing in infancy. The Institute's collaborative perinatal project and related studies are contributing particularly valuable information on norms to serve as a standard of reference from which deviations may be measured.

Testing of hearing of schoolchildren

The pilot study at the University of Pittsburgh, by grantees, undertaken to develop and evaluate the methods and techniques for testing hearing in children, as well as to help establish norms on hearing in children, has contributed valuable information this year in the area of hearing tests and diagnosis. This will be important for hearing conservation in children.

The investigators, for example, reported that in the group of children studied, there is an apparent variation in hearing sensitivity with age. Their studies also revealed evidence that hearing of children, on the average, is substantially more sensitive than the American audiometric norms by which they are presently being judged. A clear indication is demonstrated of the need for accurate hearing level measurement in children well below the American Standard Audiometrict Zero if full use is to be made of audiometry in the medical care of children. Only by such accuracy, the grantees suggest, can threshold shifts be identified and appropriate measures taken before the stage of hearing impairment for speech is reached.

Audiometric screening has not replaced medical examinations

Due to the limited numbers of ear specialists (otologists or otolaryngologists), a screening test which technicians could give, and which would identify diseases of the ear, would be an asset in casefinding. The Pittsburgh study revealed, however, that audiometric testing cannot identify all children with physical abnormalities which could lead to hearing loss. Nor do the tests identify all the children who should receive prompt medical treatment to prevent hearing loss. Some other means than an audiometric screening is needed, and for the present this points to the necessity for examinations by ear specialists (otologists). This underscores the importance of the Institute's training programs to ameliorate the shortage of such specially trained physicians.

Advances in methods of diagnosis and testing for speech

Recognition of the effect of psychological factors in inhibiting language development was strengthened this year by conclusions resulting from a report based on meetings of the American Psychoanalytic Association. However, many children have been considered mentally retarded or emotionally disturbed because of failure to recognize the actual physiological process, neurological pathway, or brain area which is failing to function properly in producing understandable speech.

Several notable advances in methods for testing and diagnosis have been reported this year. Studies of the speech patterns of cerebral palsied children by Institute grantees have analyzed difficulties of consonant sounds in terms of manner and place of articulation and voicing. It is believed that the results of this work will provide new guides for speech therapy with this special group. A series of studies on the articulation of mentally retarded children also has been conducted.

TREATMENT OF DISORDERS OF HEARING AND SPEECH

Medical and surgical progress

For one or two past generations, the treatment of disabilities of the ear was almost limited to such surgical procedures as lancing eardrums and performing mastoid operations to prevent death from a spreading brain infection. Loss of hearing was almost a secondary consideration. With the modern era of antibiotics, adequate medical care usually can prevent these tragedies, and the number of mastoid operations has dropped almost to zero.

The emphasis of surgery is now on the restorative processes—the reconstruction of the damaged drum, and especially surgery for otosclerosis. This previously incurable form of deafness is now yielding to the newly refined surgical techniques. Institute efforts are concentrating on the study of the nature of the otosclerotic process, the refinement of methods for surgical correction, and ultimately the prevention of this disorder through a more precise knowledge of the mechanisms which produce it.

A new exactness in speech therapy

In the remedial training of individuals with speech disabilities, the emphasis now is on the development of training methods which are specific to the exact disability involved.

Simultaneous recordings of motor responses of the tongue, breathing responses, visual and auditory responses, and brain activities have been made in brain-injured children suffering with language disabilities. Scientists at Northwestern University, supported by the voluntary Easter Seal Society, feel these recordings will aid in understanding the physiology of the learning processes and identifying the variations in individual auditory and visual deficiencies resulting from brain damage. Correlation of these studies should make possible more accurate diagnosis of each child's problem as an approach to treatment. It will also provide information applicable to adults suffering from aphasia as a result of stroke, cerebral palsy, deafness, and various forms of dyslexia.

Similarly, efforts are being made to refine the management of cases of cleft lip and palate of which nearly 6,000 new cases appear every year in the United States. Studies made of cleft lip and palate conducted by scientists of the National Institute of Dental Research showed an interesting association between this condition and the aborted fetal population. For a series of 3,216 aborted human embryos of 6 to 19 weeks, the prevalence was 19 per 1,000 in contrast to a prevalence rate of 1.6 per 1,000 live births.

Scientists studying mice this year, to learn the function of the tongue in cases of cleft lip and palate, found that normal palate closure is initiated by the palate shelves, not the tongue. And mice with congenital cleft lip show that mechanical stress in the tongue is altered to impede the proper movement of the palatine shelves to the horizontal position.

THE INSTITUTE LOOKS AHEAD

Research in hearing and speech involves many diversified approaches to these interrelated fields. From this report's sampling of research progress in 1963 in this rapidly expanding field can be predicted an ever-widening research effort by the Institute with a resulting intensification of practical applications for patients.

EYESIGHT PROBLEMS OF YOUNG CHILDREN

Mr. Fogarty. Now, what about problems of eyesight?

Dr. Masland. Here again it is most important that these disabilities be recognized at an early age.

For example, double vision or squinting is something that occurs in about 2 percent of the population. In this condition, the images of the two eyes are not properly superimposed, so they see double. Unless this is corrected at an early age, the individual suppresses the vision of one eye, since it is confusing to him to see double.

Mr. Fogarty. What do you mean, at an early age?

Dr. Masland. Before the age of 4.

Mr. Fogarty. Oh, that early.

Dr. Masland. Unless it is recognized at this early age, the suppressed vision of one eye will cause it to become useless, and in fact, blind. There have been recent methods of restoring vision to some extent, but it is much more effectively handled if it is treated in the first few years of life, by making the child use first one eye and then the other. It is a very simple thing to do but it has to be recognized.

Mr. Fogarty. Who would make that sort of a test? The optometrist? The pediatrician? Pediatricians certainly are not trained in this area, are they?

Dr. MASLAND. One of our concerns is to provide a very simple screening test which the pediatrician can use. The average mother takes her child to the family doctor or the pediatrician and he is the one who must do the screening.

Mr. FOGARTY. Are you working on that now?

Dr. MASLAND. Yes, we have been. Of course, again, our concern in the Institute is primarily the development of the methodology. This is the sort of thing that the collaborative project is doing—working out the methods for the early recognition of these things in order that they can be passed on to the Bureau of State Services and the Childrens Bureau to put into operation.

Mr. FOGARTY. I see.

HEARING AIDS

You mentioned hearing aids for small children. You very seldom see a small child with a hearing aid.

Dr. MASLAND. You will, more and more.

Mr. FOGARTY. There is quite a racket in the sale of hearing aids, is there not? The markup is tremendous.

GLAUCOMA

Are we making headway in glaucoma?

Dr. MASLAND. There has been some very important advances in the general field of vision research. In respect to glaucoma, the methods for diagnosis are much more precise than they were. We are now able to distinguish between disturbance of production of fluid in the eye and interference with its outflow. The pressure within the eye, which is deranged in glaucoma, is determined by a balance between the production of fluid and its absorption. In some individuals, one is apparently at fault; in other individuals, it is the other; and from the theoretical point of view, it is most important to be able to distinguish. These investigations are greatly sharpening the ability of the ophthalmologist to detect the individual whose eyesight is in danger. This, again, requires a screening test for individuals over 40; the tests that have been run indicate that about 2 percent of the population over the age of 40 has increased pressure and some risk of glaucoma. Such individuals should be recognized and carefully followed so that they can be treated if there is actual danger of loss of vision.

Mr. FOGARTY. You mentioned in your opening statement something about Dr. Kaufman. Is he here? Is he in the room?

Dr. MASLAND. No, sir. He is not here. He is not actually an Institute scientist. He was a clinical associate at the Institute. He then went into one of our training programs in Boston under the ophthalmology training program, and now he is in Florida, heading up one of our training programs. This is the speed with which this field is developing.

Mr. FOGARTY. It did not get off the ground for several years, did it?

Dr. MASLAND. That is true.

Mr. FOGARTY. They did not do anything.

Dr. MASLAND. Actually, Mr. Chairman, the Institute's contributions in the field of vision have been really very significant ones.

Mr. FOGARTY. Tell us about some of them.

RETROLENTAL FIBROPLASIA

Dr. MASLAND. The committee, I think, is well acquainted with them. I would like to put them on the record because most of our research consists of small advances, here and there, which raise the general level of medical care. It is only occasionally that you have a clearcut contribution for which the impact can be measured in dollars and cents, if you can measure human misery in those terms; but we might go back, first, to the retrolental fibroplasia study.

At the time the Institute's program was launched it was suspected, but unproven, that this blindness was due to oxygen. A group was called, and in spite of this suspicion, the consensus was that no one would be willing to withhold oxygen from a premature baby. As a result of the study, which was supported by the Institute and carried out under the direction of this committee, in the course of a year, it was clearly demonstrated that overuse of oxygen was dangerous for the premature child. When that result was reported, within the course of a year, the frequency of retrolental fibroplasia dropped from approximately 2,000 cases a year to almost zero. Today there are very few cases of retrolental fibroplasia occurring.

Mr. FOGARTY. But some of this basic work was done on animals in other countries?

Dr. MASLAND. That is right.

Mr. FOGARTY. I know in England, they did some of this work with guinea pigs.

Dr. MASLAND. That is right. But it had not been verified in humans, and the evidence for this was in the study itself. In the early phases of the study, in hospitals where the study was being conducted, there was great difficulty in preventing people from turning on the oxygen for prematures for whom oxygen was being reduced. Half the babies were given supplemental oxygen, and half were not. People would sneak into the nursery and turn on the oxygen because they said it was wicked to be withholding it from these babies.

At the end of the study, the reverse was the case; people were creeping in and turning it off.

It has been estimated that it costs at least $1,000 a year to take care of a blind person. This is probably a very conservative estimate.

Mr. FOGARTY. I think it is, too. I don't know how you can do it.

Dr. MASLAND. If you consider 2,000 children blinded by retrolental fibroplasia in 1 year, and estimate that each one is going to live 50 years, on the average of $1,000 a year, the cost will be $50,000 apiece. Each year that this study advanced our knowledge of retrolental fibroplasia, the country has been saved $100 million. The total expenditure for research in blindness in the years since the Institute was formed has been $65 million.

Mr. FOGARTY. I think that is your best example.

Dr. MASLAND. We have another one.

Mr. FOGARTY. As good as that one?

HERPES CONJUNCTIVITIS

Dr. MASLAND. Two years ago, Dr. Kaufman, of whom I spoke, established the value of a drug for herpes conjunctivitis.

Mr. FOGARTY. Are there various forms of conjunctivitis?

Dr. MASLAND. Yes; there are a number of forms. This particular one is caused by a virus. Now, the drug which he used, IDU, has a rather interesting story.

This drug was developed in connection with the cancer research program, by a scientist who was interested in the effects of drugs on RNA synthesis. It was hoped that this drug would be useful for the control of cancer. A quantity of it was produced under contract with the Cancer Institute. Dr. Kaufman recognized that multiplication of viruses resembled the multiplication of tumors, and developed the thesis that if this drug would prevent the multiplication of tumors, maybe it would block viruses. He tried it in rabbits infected with herpes virus and it worked. Then he tried it in humans and it also worked in humans.

Now, evidence indicates that in a person with herpes conjunctivitis——

Mr. FOGARTY. How does that affect your eyes?

Dr. MASLAND. In a considerable number of patients, it causes a corneal opacity, so the eye becomes blind. At the present time, over 2,000 people a year have to have a corneal transplant in order to see.

Mr. FOGARTY. Does high blood pressure have any connection with this?

Dr. MASLAND. No, although it is related to a number of other blinding diseases. Now, as a result of the Kaufman treatment, about 90 percent of people with herpes infection can be prevented from losing their sight.

Mr. FOGARTY. What is the first symptom?

Dr. MASLAND. Pain. It is a very painful condition. Pain, and reddening of the eye. Then there is a little blister that forms on the clear part of the eye, like a fever blister. It is a fever blister on the eye, and it causes inflammation.

Mr. FOGARTY. If you have it, you really know you have it?

Dr. MASLAND. It is terribly painful. It is not like glaucoma. Glaucoma is insidious. You can lose your vision from glaucoma before you realize it, but with this, you know you are sick.

TOXOPLASMOSIS

In the field of vision, we have been working with toxoplasmosis. Between 2 and 3 percent of all individuals are blind because of toxoplasmosis. It is a parasite rather like the malarial parasite. There has been considerable improvement in the treatment of this condition and when individuals are treated early their vision may be saved by the use of an agent developed to treat this disorder.

In the field of vision, there have also been other important new developments. There is a condition in which the retina becomes detached from the back of the eye. If this persists, the individual becomes blind. Some years ago, it was discovered that if you put a little scar around the edge of this place where the retina is coming loose, an inflammation forms and the retina becomes glued in place. The process is then arrested.

The most recent discovery is that this can be done by shining a very bright light through the front of the eye and burning a little spot on the retina. Now, new instruments are being developed which concentrate a very hot source of light on a very small spot, to improve the efficiency of this process, and a great many people are having their vision saved by this.

PROGRESS IN DISORDERS OF VISION

Mr. FOGARTY. You are really making some remarkable headway on problems of vision then, are you not?

Dr. MASLAND. Yes. And some of the additional developments are included in a more detailed report.

(The report referred to follows:)

SPECIAL REPORT: DISORDERS OF VISION

THE PROBLEM

When light strikes the eye, it passes through the transparent cornea, pupil, and lens of the eye, then through the jellylike vitreous humor, to the retina. Here it is caught by tiny photoreceptors, converted into electrical impulses and sent along neural pathways to the brain.

The many parts of the eye are vital to the process of vision, and each is subject to disease, injury, and improper development. Many eye disorders are classified according to the part of the eye affected. To learn more about the function of each part individually, as well as their interrelationship in health and disease, ophthalmologists, physiologists, chemists, and a host of other scientists are conducting a broad range of research studies.

There are nearly 400,000 legally blind people in the United States, half of them over 65 years of age, and more than 100,000 who cannot read ordinary newsprint, even with the aid of glasses. With special attention to our aging population, which increases yearly, research must find a way to stop the mounting incidence of blindness.

The magnitude of the country's stake in health research is strikingly illustrated by the Institute's experience with retrolental fibroplasia. In 1953 the Institute provided partial support for a cooperative project to verify the suspected relation between overdosage of oxygen in premature infants and the occurrence of RLF. The cost to the Institute of this investigation was $35,000. By 1954, a year later, this study unequivocably demonstrated the existence of this causal relationship, and the use of excessive oxygen was promptly discontinued across the country. The incidence of blindness due to RLF dropped from an annual rate of 1,888 to 28 in a few years. For each individual whose vision was saved by this program, the minimum saved to this country is well in excess of $1,000 per year, not including loss of productivity. For each year that this study advanced the discovery of this causal relationship, the country has saved $1,860,000. In a life span of 65 years, therefore, the care of the children spared from blindness by advancing this discovery even 1 year would have cost the Nation more than $100 million, or more than twice the $40 million spent by the Institute for vision research since its establishment in 1950. These estimates, of course, are in terms of economic values only. The benefits in terms of human values are incalculable.

Other advances have come through research and training made possible by the Institute. Two years ago an Institute trainee and previous staff member discovered a drug cure for herpes keratitis, a viral infection which often leads to blindness. The cure is thought to be the first successful treatment of a virus disease in man, and has already led to other, similar treatment of virus diseases in the eye. Further study of the mechanisms by which the new drugs, IDU and cytosine arabinoside, act may lead to improved treatment of patients with viruses in other parts of the body.

The relative importance of the different causes of blindness has changed drastically during the past few decades. Many infectious diseases can now be treated with antibiotics and other drugs not in existence 50 years ago. On the other hand, chronic disorders of aging present a growing problem as more people live beyond middle age. Cataract and glaucoma together account for one-third of all blindness in the United States today.

In addition to disorders that limit themselves to the eye, there are many ocular complications of diseases affecting the body as a whole. Thus, in some instances impairment of vision may be the first indication of the development of systemic disease, and the ophthalmologist may be called upon to establish the diagnosis. On the other hand, it is equally important to recognize that ocular complications may develop during the course of such recognized systemtic disorders. The patient with diabetes, hypertension, arteriosclerosis, and other general chronic disorders should regularly see his ophthalmologist for possible eye complications.

Because eye involvement in these disorders cannot be isolated from the general disease, eye research must be done in cooperation with other specialties. To meet this need for a multidisciplinary approach to neurological and sensory disease problems, the Institute has established a number of program project grants. These program projects are large grants, awarded to institutions for the support of broadly based and usually long-term programs of research.

The Institute is supporting four program projects in vision research, at the University of Chicago, the Retina Foundation in Boston, the State University of Iowa, and Columbia University in New York. Here are gathered many research physicians and other scientists from such related scientific areas as pharmacology, physiology, chemistry, electrophysicology, anatomy, immunology, and pathology.

Similar to the program project is the clinical center grant. Under this program the Institute offers support to medical institutions engaged in a multidisciplinary attack on specific eye diseases or in a correlated attack on a group of eye diseases.

Another type of cooperative study is the paired grant. This concept takes advantage of resources and specialized skills of researchers in other countries. Grants on different aspects of the same problem are awarded simultaneously to an American and a foreign institution and the work of the two combined for a better understanding of the overall problem.

The first paired grant in ophthalmology was awarded last year to the State University of Iowa and to Uppsala University in Sweden. These two institutions have launched a multidisciplinary attack on the problems associated with glaucoma.

The Institute has given priority to the training of professional personnel for academic and research careers. Before establishment of the Institute, ophthalmology had traditionally been a clinical science. Teaching in the field was mainly limited to undergraduate demonstrations and clinical training in a number of residency programs. Research, although of a high quality, was limited principally because of a lack of manpower.

The Institute's ophthalmology training program, launched in 1952, has now produced approximately 750 highly trained research specialists. In the last 8 years the number of full-time ophthalmologists has increased from 2.2 ophthalmologists per 100,000 persons to 3.3, an increase of 50 percent. The number of such men in full-time academic positions is steadily increasing.

Last year Institute training grants to 37 institutions provided training in ophthalmology for nearly 350 individuals. Approximately 200 of these received stipends. Fellowships and other types of individual awards brought the total participants in the Institute's training program to 386.

GLAUCOMA

One-seventh of the blind population in this country, 57,000 Americans, are blind because of glaucoma. Ninety-five percent of them are over 40 years of age. Although the growing number of older people may increase the incidence of glaucoma, early diagnosis and improved treatment will now make it possible to prevent blindness in a large number of cases.

Glaucoma occurs most frequently in the simple chronic form, which may slowly destroy vision without warning. This type occurs most frequently among relatives of glaucoma victims and in persons over 35 years of age. Glaucoma may also occur as a result of another infection or disease, or in an acute form which attacks suddenly and painfully.

In glaucoma, the aqueous fluid which normally flows through the eye fails to drain out as readily as it forms. Instead, the pressure builds up until it presses against the nerve fibers and blood vessels feeding the retina and optic nerve. If glaucoma goes unchecked, the field of vision may become smaller and smaller until blindness results.

Diagnosis as well as treatment of glaucoma depends on being able to measure the intraocular pressure and keep it below damage levels. Detection of abnormal pressure is complicated by a normal pressure variation throughout the day and from one day to another. Several pressure-taking devices, known as tonometers, aid in evaluating pressure. The Schiotz tonometer, a small instrument that can be held in one hand, is in wide use, especially in glaucoma detection surveys. However, the more complicated applanation tonometer is more accurate and is now routinely used by the ophthalmologist.

A complicating problem in intraocular pressure measurement is a factor called ocular rigidity, which affects readings on the Schiotz tonometer. Numerous studies have revealed ways to make allowances for this factor and to improve measurements with the Schiotz tonometer.

Institute studies on glaucoma include clinical and laboratory investigations on fluid exchange in the eye, patency of the outflow channels, rate of fluid formation and ways to influence these factors.

Physiologists, pharmacologists, biochemists, and ophthalmologists of the Institue also have investigated the role of blood vessels in the regulation of eye pressure, pressure variations due to nervous and other factors, response of vessels in the eye to drugs, the ability of certain drugs to stimulate or block nerve endings, and the effect of enzymes on fluid formation. Some of these studies have been clinical, but most have involved animal research. Many patients have profited from these integrated investigations, and it has been possible to control eye pressure for long periods of time.

The presence of large quantities of gamma-globulin containing plasma cells near the trabecular meshwork in 75 percent of glaucomatous eyes as compared to only 20 percent in "normal" eyes is an indication, Institute grantees believe, that antibodies must be present at some time during the glaucoma process. The significance of such antigen-antibody reaction is not yet clear, but since any alteration in the trabecular meshwork may affect outflow of aqueous fluid, its structure and function are important to the study of glaucoma.

Since prevention of blindness from glaucoma depends on control of the pressure inside the eye, scientists are constantly seeking better methods of measuring and evaluating pressure rise, especially in the early stages before symptoms appear. For this reason scientists were encouraged this year by a development with steroids which promises to provide a new aid in diagnosing glaucoma.

Concerned with reports that long-term use of steroids may cause glaucoma, investigators applied steroid drops to the eyes of volunteers and glaucoma patients. They discovered that not only did steroid drops produce a rise in intraocular pressure (the hallmark of glaucoma), but also the increase in pressure was greatest in glaucomatous eyes. Relatives of glaucoma patients also responded with a greater increase in pressure. These findings suggest that steroid drops in the eye, together with provocative tests, may aid in diagnosing the chronic type of glaucoma before damage occurs to delicate eye tissues. It has already been proved capable of unmasking hypotensive glaucoma, a particularly insidious type not detectable by the usual pressure-measuring techniques of tonometry and tonography.

Steroid-induced changes in the eye resemble chronic glaucoma in all but one respect: they are totally reversible; that is, when drops are discontinued the eye returns to normal. Therefore, steroids may provide a safe means of producing glaucoma in one eye and comparing the results with the normal control eye of the same person. The fact that only the eye treated with steroid drops shows an elevation of pressure already has shown that the steroid effect is a local one and is not due to systemic changes, such as a change in the blood pressure.

While physicians and patients have been warned against the use of steroids in the eye without vigilant medical supervision, research ophthalmologists are seeking ways to secure the valuable anti-inflammatory effects of these drugs while guarding against their adverse side effects. Finding the lowest effective concentration of the drug may be one way of accomplishing this.

Observations on a strain of rabbits with buphthalmia, an inherited type of glaucoma, have given scientists clues to the sequence of changes that take place in the eye as it develops glaucoma. Their studies revealed that the ability of the aqueous to leave the eye is decidely impaired early in life. It was also shown that this impairment of outflow is at first compensated by less secretion of aqueous, but that as this mechanism fails, pressure elevation develops and is eventually followed by ocular damage in the usual form.

In further experiments on rabbits, scientists will examine the ability of drugs for the treatment of glaucoma to prevent ocular damage. They will also attempt to determine whether maintenance of lowered secretion will prevent the development of buphthalmos; and they will study the role of early glaucoma surgery.

In addition, studies are planned for the earlier detection of glaucoma in these rabbits inheriting glaucoma.

These and other studies, adding to our knowledge of glaucoma, are making treatment more effective and bringing us closer to the possibility of preventing all ocular damage from elevated eye pressures.

CATARACTS

Cataract, a clouding of the lens of the eye, may be caused by congenital defects, injury, aging, radiation, toxic agents, or metabolic disorders. The most common type, senile cataract, is linked to the process of aging that alters metabolism and builds up insoluble proteins. Research at the Institute and elsewhere is aimed at a better understanding of the mechanism in cataract formation. Although sight can be restored after the surgical removal of the cloudy lens, scientists hope that research may lead to methods of prevention.

Cataract surgery today is a simple procedure, especially in the aged. The operation has been made easier in the past few years by the use of an enzyme, alpha chymotrypsin, to dissolve the fibers holding the lens in place. Even with the aid of eye glasses, or contact lenses, however, the eye without its natural lens does not see as well, and the research goal of prevention is still important.

Cataracts in children are often congenital, being associated with basic defects in the developing embryo, with illness of the mother during pregnancy (German measles, for instance), or with metabolic defects such as congenital galactosemia. Children's cataracts present special problems: Removal is necessary to assure normal development of other parts of the eye; and surgery is more difficult because the fibers holding the lens in place are harder to break. Revival of an old method now allows the surgeon, in special cases, to use "needle aspiration" to draw the opaque lens out of the eye.

Cataracts have been produced in animals by dietary deficiencies in essential amino acids, as well as will diets high in certain forms of sugar. Much has been learned by observing these clouded lenses under the microscope at various stages of growth and opaqueness. Some cataracts begin in the core or nucleus of the lens and grow outward, while others are formed in the outer rim and spread toward the center.

While protein and enzyme chemists at the Institute have worked on various basic aspects of lens chemistry, other research specialists have observed changes in the individual cells of the lens, particularly those changes produced by radiation. To comprehend the abnormal process which takes place during cataract formation, scientists studied the lifespan of the cells, how they multiply and proliferate, and their characteristics under the high magnification of the electron microscope.

Last year it was reported that triparanol (MER–29), a drug widely used to reduce cholesterol in cardiac patients, caused cataracts. This has been proved by producing cataracts in rats fed triparanol. Institute scientists are now investigating the possibility that abnormal cholesterol metabolism in the lens may produce cataract.

Institute grantees recently have helped to put forth a new and important theory on the formation of cataracts caused by an accumulation of certain forms of sugar in the lens. This osmotic theory suggests that sugar penetrates the lens fibers and is reduced to its alcohol derivative. In this form it cannot diffuse out of the fibers or be metabolized, and thus it becomes locked in the lens. As the concentration of sugar-alcohol increases, water moves into the lens osmotically, causing swelling, bursting, and eventual disintegration of the fibers.

One grantee, who has learned how to keep the human lens alive in a test tube, has recently made a study of the way amino acids enter the lens to form the proteins which make up one-third of its content. Since cataract formation involves an accumulation of insoluble proteins, it is important to learn as much as possible about the behavior in the lens of amino acids which are the building blocks of proteins. Using a radioactive label, one investigator traced the movement of amino acids from the surrounding fluid into the lens. He also studied the accumulation of amino acids in the lens, which takes place not by simple diffusion but by an active transport system which keeps the accumulation in balance. Further studies to elucidate the transport system revealed that the mechanism is located in the lens capsule and outer layer.

The same investigator later found that the lens and surrounding aqueous fluid of diabetic rats contained a lower concentration of amino acids than those of the normal eye. He suggested that a defect in the transport mechanism for accumulating amino acids in the lens may be responsible for cataracts associated with diabetes.

RETINAL DISORDERS

The retina is a highly complicated and vital part of the process of vision. When light falls upon the retina, the cells undergo chemical changes which eventually lead to the generation of nerve impulses. These nerve signals travel from the eye to the brain and there evoke changes which result in the process of vision.

Among the many kinds of nerve cells in the retina, the photoreceptors, the rods and cones, are most important. Cones are located in the central area of the retina called the macula and provide vision to read and to distinguish color. Rods, on the other hand, register black and white and are important in dim light where colored objects appear as light or dark.

Both rods and cones contain visual pigments which absorb light. Techniques have been developed to measure the amount of pigments present under different conditions and to evaluate the relationship between this concentration of pigment and ability to see. Study of these pigments has also advanced our understanding of color vision and color blindness.

It has been known for some time that electric currents are generated by the retina when light falls on it. Analysis of relations between light and current has shown that a number of processes (chemical reactions and electrical changes) must occur before nerve impulses can be generated. Efforts are now being made to understand the nature and properties of these processes.

Organization of nerve signals in the optic nerve and pathways to the brain have also been studied. In order to produce a sensation reflecting the external world, the impulses generated by the eye must be organized in a meaningful and orderly manner. Scientists have tried to discover what rules are followed to accomplish this complicated task. It has been seen that different nerve cells in the retina are sensitive to different shapes or patterns of the image. Some are activated by lines, some by curves, and some by movement. These and many other physical, chemical, and psychological studies give a better understanding of the normal processes underlying vision.

In order to understand and treat disorders of the retina, it is necessary to measure the field of vision, or the extent of the functioning retina. The past decade has brought great improvements in perimeters and tangent screens, instruments used to chart the visual fields.

A research technique for judging the function of the retina is the electroretinogram (ERG), a recording of the electrical response of the retina to light stimulus. The ERG is especially useful in evaluating vision in children, the emotionally disturbed, and others who cannot cooperate with the tester.

Aided by computers, which enable scientists to get a much more selective response, Institute and grantee investigators have refined ERG measurements enabling them to predict the future course of a complex group of degenerative diseases of the retina including retinitis pigmentosa. Extension of these studies to the hereditary characteristics of these diseases provides a basis for genetic counseling and planning. Unfortunately, none of these studies has turned up leads that might prevent the progression of the degenerative process in retinitis pigmentosa.

Since the ERG distinguishes and measures rod and cone function in the retina, Institute grantees this year used it to describe a cone dysfunction syndrome. The syndrome was established through findings on 47 patients with diminished vision, defective color vision and an ERG indicating no cone function. These findings will help distinguish those patients with cone malfunction from those with similar symptoms caused by different conditions.

Retinal detachment, separation of the retina from the adjoining choroid and its own outer layer (pigment epithelium), is a frequent ophthalmological problem. The condition can be corrected by creating a scar which seals the retina in place as it heals. The adhesive lesion is usually produced by a diathermy electrode. This procedure is often combined with scleral buckling, in which the sclera is pinched off to make a smaller globe before the torn retina is pushed back into place against the choroid.

A recently developed treatment for retinal detachment consists of directing a strong light through the dilated pupil to cause a small lesion. This treatment is useful in closing small retinal holes or tears before the retina becomes detached. It is also used postoperatively to reattach small areas.

A promising refinement of the light coagulation technique is under study by grantees. Lasers, light rays of incredible power and sharpness, can be focused to a point narrower than the edge of a surgeon's scalpel, which may prove more accurate in sealing the retina in place. Use of the laser to cure retinal detachments has been successful in a few patients, but it is too early to tell whether it is superior to other forms of photocoagulation.

This year, instead of sealing the retina back in place by diathermy or light coagulation, Institute grantees report the use of freezing to produce adhesive lesions with sharper, clearer borders. These preliminary findings require confirmation, but it is possible that the freezing technique may be employed not only for safer repair of the retina, but also for cataract and other types of ocular surgery.

The treatment of retinal detachments may also be aided by a renewed interest in the composition and function of the vitreous, the jelly-like mass which fills two-thirds of the eyeball. It has been known that detachment is preceded by a break in the retina which allows seepage of this fluid between it and the pigment epithelium. A grantee study this year revealed evidence that the vitreous plays an indispensable role in the formation of some types of retinal detachment.

The use, by grantees, of liquid silicone to replace the vitreous has proven helpful in curing some otherwise hopeless cases of retinal detachments. The transparent silicone remains in liquid form and helps hold the retina in contact with the choroid. Being chemically inactive, it seems to produce no immune reaction from surrounding tissues. The procedure cannot be recommended for widespread use until the results have been observed over a long period of time, but encouragement can be gained from one case now 2 years old.

The thalidomide tragedy has alerted the profession and Institute investigators to the danger of unforeseen toxic side effects of compounds which are often extremely useful in the treatment of systemic or local diseases. The MER–29 problem has been mentioned before. Also under study is the irreparable injury to the eye of patients on long-term chloroquine therapy. These drugs have been widely used to treat discoid or systemic lupus erythematosus, severe rheumatoid arthritis and other diseases. Institute scientists established methods of early diagnosis of chloroquine damage to the eye and cooperated with grantees on chloroquine metabolism studies which led to efforts to increase the elimination of the compound from the body tissues. Further studies are necessary to determine whether this approach will in fact prevent the progress of the disease.

Chloroquine is still the most effective treatment for certain diseases, and because of these findings, caution can now be exerted to prevent these visual complications of prolonged treatment.

INFECTIONS

Corneal infections

Diseases of the cornea (the clear tissue in front of the pupil) lead sometimes to dense scar formation which reduces vision to bare light perception. Transplantations of clear corneas from eyes of patients or eye bank material are often successful in restoring sight. In some cases physicians have been able to halt the clouding process of the natural cornea by grafting on a new piece of cornea.

Institute-supported studies have developed several dehydration and freezing methods for preserving corneas for corneal transplantation. Long-term storage and ease in shipping these preserved corneas have enabled doctors to perform corneal transplants to restore the sight of numerous people in other countries as well as in the United States.

Corneal tissue has been under study by several Institute investigators to discover why the transplant sometimes becomes cloudy several months after the operation. One investigator found evidence that the clouding may be due to an immune reaction of the eye to foreign tissue. Another observed that frozen corneal tissue causes less foreign body reaction than do fresh corneas. Still others have experimented with different methods of thawing frozen corneas. Optic clarity of the graft has also been found to be affected by temperature at which frozen corneas are stored. All of these factors have a bearing on the success or failure of the corneal transplant operation.

Institute studies revealed that two portions of the cornea seem to be involved in such transplant failures: The inner lining of the cornea and its collagen fibers. To learn more about why transplants become opaque, the inner lining of the cornea is being examined under the microscope and its growth pattern and cell population studied. A greater understanding of the manner in which cells divide and grow will aid in preventing improper growth that may result in an opaque cornea. In addition, studies have been initiated to investigate the chemistry of the cornea, with special reference to its collagen fibers.

Only one type of transplant operation, half-thickness or lamellar transplantation, can be performed with preserved corneas. For the full-thickness corneal transplant, fresh corneas are needed. Neither of these methods is successful in cases of dense scarring. For this reason, scientists have been trying to develop an artificial cornea to be used instead of a natural transplant. Last year, two laboratories reported successful use of plastic corneas in rabbits and rhesus monkeys; use of such transplants for humans is still not perfected.

A federation of 35 eye banks to collect and store corneal tissue for transplants was recently organized under the auspices of the American Academy of Ophthalmology and Otolaryngology to coordinate activities of its member banks, stimulate donation of eyes, establish national legislation on eye donations, and encourage and finance research in the prevention and treatment of eye diseases.

Treatment of corneal infections is dependent upon early diagnosis by which the viral, bacterial, or fungal nature of the infection can be established. This Institute has recently cooperated with the National Institute of Allergy and Infectious Diseases in improving methods of identifying these diseases and curing them through drug therapy. It has been known for several years that fungal and viral infections of the eye are made worse by steroid treatment. More accurate diagnosis of these diseases will help in preventing deleterious affects from steriods.

Progress in treating virus infections of the cornea by the use of an antimetabolite, IDU, stimulated workers at the Institute to cooperate with the Division of Biologic Standards to investigate other compounds which may be able to destroy viruses. It is too early to evaluate these results, but a grantee has reported discovery of another antiviral agent, cytosine arabinoside. This new drug is equally as potent as IDU and acts against viruses resistant to IDU.

Uveitis

Uveitis is an inflammation of one or all three parts of the uveal tract, comprising the iris, choroid, and ciliary body. A mild form, nongranulomatous, commonly involves the iris and ciliary body, and because these tissues are in front of the eye, this form is sometimes called anterior uveitis. Inflammation of the choroid often involves the retina also, and is therefore called chorioretinitis; this is usually granulomatous, the more serious form of uveitis.

Although nongranulomatous uveitis is an inflammation of the eye, no pathogenic organisms have been demonstrated in the tissues to account for this inflammation. Evidence of its inflammatory nature is further strengthened by the observation that it may be influenced by steroid therapy—a treatment known to reduce inflammatory processes. An autoimmune form of sensitization has been suspected. Granulomatous uveitis usually follows active microbial invasion of the tissues by the causative organism (e.g. mycobacterium tuberculosis, or toxoplasma gondii). However, these pathogens (organisms causing the inflammation) are rarely identified by laboratory tests, and a definite etiologic diagnosis is seldom possible. Treatment, therefore, is often based on careful and elaborate clinical and laboratory examinations which narrow the possibilities to one or two probable causes.

Several years ago Institute scientists discovered that one cause of granulomatous uveitis was toxoplasma gondii, a protozoan parasite. Since that time many patients have been successfully treated for toxoplasmosis. Over the years Institute investigators have developed the roper drug dosage for effective treatment of patients with toxoplasmic infections without serious side effects.

Trachoma

Although trachoma is not a large problem in this country and antibiotics to prevent secondary infections have reduced the incidence of blindness, it is still the leading cause of blindness for the world as a whole. Institute grantees have been working for several years to develop an effective vaccine against trachoma. Trial vaccines administered to a group of preschool children on Taiwan gave overall protection of about 60 percent.

These studies, plus others using the Taiwan monkey as an experimental model, have led the investigators to postulate that trachoma is a recurring disease, and that the more severe progressive trachoma infection occurs only after reinfection. During some 400 trachoma infections in monkeys considerable information on pathogenesis of the disease was developed, and recently, by newer methods of immunization scientists succeeded in completely preventing infection.

TUMORS

Tumors of the eye threaten the life of the patient as well as his vision. Early discovery may save both, since in their initial state some neoplasms are amenable to treatment or surgical removal. Treatment usually consists of X-rays, and in some types of tumors this is combined with radiomimetic drugs which resemble radiation in their biological action.

Other antitumor agents, called antimetabolites, interfere with the normal metabolism of cells and have been used in rare cases to eradicate malignant tumors in the eye. Present Institute studies are attempting to determine how these compounds affect tissues in the eye, since some of them have been shown to produce cataract. With further study the antimetabolites may prove useful, not only as weapons against ocular tumors, but also for treating a type of uveitis in which an autoimmune mechanism may be operative.

AMBLYOPIA

Some 4 million people in the United States are deprived of normal function in one eye because of amblyopia, a reduction in vision which cannot be relieved by glasses and is not dependent upon visible changes in the eye.

Amblyopia (sometimes called amblyopia ex anopsia) may exist at birth or be acquired soon afterward. It results under circumstances leading to lack of use of one eye. It may be due to muscular imbalance, refractive error, or other defect present when the infant is still learning to focus his eyes. A child may have eye trouble that causes him to see a double rather than single image. When his attempts fail to get these two separate pictures to come together, he tends to suppress the weaker eye and use only the stronger one. When this becomes a habit, the vision in the weaker eye is gradually lost or fails to develop properly.

Correction of amblyopia in the young consists of placing the good eye at an optical disadvantage and forcing the child to use the squinting eye. This may be done by patching the good eye, by exercises, or by blurring the retinal image of the sound eye.

If amblyopia is discovered before the age of 3, treatment and correction of the underlying muscle imbalance or other cause is usually successful. Between the ages of 3 and 6 there is still a good chance of success, but after age 6, present treatment has resulted in improvement for only a small percentage of cases. Therefore, the greatest hope for this disorder lies in early discovery.

Recent developments make it possible to offer hope even for adults with amblyopia. Grantees this year report dramatic success in a few highly motivated patients with the aid of the new technique of pleoptics.

Pleoptics in its various forms attempts to overcome the sluggishness of the macula (area of sharpest vision on the retina) with strong intermittent light stimulation. Institute support of research on pleoptics has brought gratifying results. Using recently developed pleoptic instruments, grantees this year were able to achieve usable vision in the amblyopic eye of patients who through an accident had lost the vision of their good eye. Without pleoptic treatment these patients would have had almost no useful vision.

NORMAL PROCESSES OF GROWTH

Understanding the normal processes of growth is always a necessary part of studying and curing disease. Embryological studies by Institute scientists have made possible a partial reconstruction of the probable sequence of events in the development of the chick eye. As the embryonic chick eye becomes a closed globe, vitreous substance accumulates and begins to exert pressure on the walls of the globe. At this point in development, the eye, except for the lens, begins to resemble a balloon with many layers. The outermost, the sclera, is a tough, fibrous layer. Next is the choroid, which carries blood vessels to and from the eye. The innermost layer is the retina, the actual light-sensitive tissue.

Of interest in recent investigations have been the two layers of the retina. The innermost is the neural layer, which contains the cells that translate light energy into nerve impulses together with a few layers of neurons that begin the trans mission of these impulses to the brain. In back of the neural layer is a pigmented layer of cells that may serve a variety of roles in different animals in absorbing and reflecting light.

Previously it was found that the neural layer increases in area at its own growth rate, with the pressure of the vitreous humor maintaining a globular shape. The pigmented layer, however, does not increase in area at its own rate but responds to the tension exerted on it by the neural layer.

While this general sequence of events holds true for the development of eyes in all vertebrates, the details of similarity and difference require further study.

A factor has been demonstrated, but not yet characterized, which is necessary for the growth of the lens during embroyonic development. Present evidence indicates that this factor probably originates in the neural retina. Another factor, possibly the same one, is necessary for the elongation of lens cells to form lens fibers—a vital part of lens growth because most of the lens is composed of fibers formed by elongation of cells from the outer rim of the lens.

The development of surgical techniques which permit the removal and replacement of the embryonic lens has permitted an unequivocal demonstration that the lens not only induces the cornea of the eye but is also essential for its continued differentiation and maintenance throughout an appreciable period of development.

The technique of cell tissure culture has been used to study the elongation of lens cells into lens fibers in an isolated and carefully controlled environment. These studies promise to define the factors and conditions essential for elongation of lens cells and make it possible to identify the origin of the constituents of the vitreous body.

Other Institute studies, reported last year, postulate that the inherent elasticity of the choroid coat of the eye helps to determine its final shape and counteracts part of the intraocular pressure. The investigators believe this factor may have importance in abnormalities of refraction, which make it necessary for some persons to wear glasses.

Another study of normal processes indicates infants have remarkably good vision and eye coordination in the first 10 days of life. It has been commonly believed that babies cannot see little things and cannot make both eyes work together in the first 6 weeks of life. The new findings may enable doctors to evaluate and treat eye diseases when disorders can be most effectively corrected.

AIDS TO THE BLIND

The past few years have witnessed a renewed effort to develop devices which will reduce the social isolation and physical handicaps imposed by blindness.

Proceedings of an international conference held last year to study means of using technology to help the blind report a number of developments. Among these are the electronic cane and other devices to aid the blind in moving about: talking books and other devices to provide information to the blind; braille and other tactile reading techniques; and use of the remaining sensory channels to compensate for blindness.

A few devices have been developed to convert optical images into sounds, but science is still some distance from producing a practical reading machine which any blind person may have in his home. Research is continuing.

A number of mobility devices which detect objects by electromagnetic waves or sound emission have been constructed. The most sophisticated version detects more than 95 percent of objects most commonly encountered in travel. Terrain changes in the form of curbs and stepdowns have proved difficult to detect. Although two laboratory prototypes have been designed which warn the user of small terrain changes, much work needs to be done before they become compact, lightweight, and reliable. For the time being, the cane seems to be the more practical device.

Braille, which has provided reading material for the blind for many years, recently has been improved and its production made easier by the use of computers and automation. Less than 25 percent of all blind people learn braille, however, and for this reason long-playing talking books and, more recently, the tape recorder, have begun to play a larger part in the task of supplying information to the blind.

Science has also begun to explore the performance of tasks, such as seeing and hearing in living beings other than man, in the search for a better understanding of the basic principles underlying sensory loss.

MODEL REPORTING AREA FOR BLINDNESS STATISTICS

Progress is being made in the Institute's model reporting area to obtain better statistics on blind persons in the United States. Organized in 1962, the project now has nine member States, each maintaining a statewide register of blind persons. The registers employ a common definition of blindness and record sex, age, race, and degree and cause of visual loss. The Institute has provided technical and, in some cases, financial assisatnce to 13 additional States interested in revising their registers to meet the standards of the model reporting area.

As membership expands, and as annual tabulations derived from member registers become available to the Institute, it should be possible to compile the most accurate statistics on blindness yet available. Plans are underway to publish 1962 data from member States. The report will reflect the number of additions to the registers (incidence) as well as the total number on the register at the end of the year (prevalence).

The program, which is a cooperative endeavor of the Institute and the member States, has the support of voluntary health agencies and the Division of Chronic Diseases. It has facilitated widespread adoption of the Standard Classification of Causes of Severe Vision Impairment and Blindness prepared by the National Society for the Prevention of Blindness. Also up for adoption is a standard eye report form. Adoption of this form and the standard classification will help solve the longstanding problem relating to differences in terminology used in classifying blindness according to cause.

The blindness registers being maintained by the member States have a strong potential as research tools. The Institute has already initiated two research projects utilizing State blindness registers. They deal with the etiology of blindness in children and survivorship among the blind.

Institute research on visual disorders covers a broad range from the study of individual cells to the effects of drugs on the course of disease. Future research is expected to show a trend toward an even broader approach and to contain more interdisciplinary studies. Some of the problems relating to drug therapy have recently pointed up the interrelationships between eye disorders and general systemic disease. Broad-based studies, such as those carried on under program-projects, will probably play an increasingly important role in the study of visual disorders.

CEREBRAL PALSY

Mr. FOGARTY. Tell us what you are doing in the cerebral palsy area. You may put that in the record.

Dr. MASLAND. I have a special report on that.

Mr. FOGARTY. We will put that in the record then.

(The special report on cerebral palsy is as follows:)

Special Report: Cerebral Palsy

THE PROBLEM

Cerebral palsy affects a half million people in the United States. There are about 6 cerebral palsied infants in every 1,000 live births. As the babies of the postwar boom mature and have families, an increase of more than 100,000 children with cerebral palsy during the next 10 years can be predicted. However, measures to prevent or alleviate the damage should reduce these figures and lessen the impact on afflicted individuals and on our society. Cerebral palsy is not a single disease, but includes a number of conditions in which brain damage results in physical or muscular disability. It is a chronic condition, because no method now exists for restoration of damaged brain tissue. Treatment is directed toward the consequences of the brain damage. Methods of prevention are sought.

A PRIMARY INTEREST

Research on cerebral palsy has been central to the program of the National Institute of Neurological Diseases and Blindness since the inception of the Institute. This primary interest is reflected in a major program—the collaborative project for the study of cerebral palsy, mental retardation, and other neurological and sensory disorders of infancy and childhood, a joint endeavor of 15 medical centers and the NINDB.

The Institute's research program with rhesus monkeys in Puerto Rico has paralleled the collaborative project in studies of perinatal factors in brain damage to the newborn. In fiscal year 1963, awards of 44 grants were made in the total amount of $7,560,000 for cerebral palsy research. As of January 29, 1964, research awards had been made for 38 studies in the amount of $7,600,000; thus, grant-supported research on cerebral palsy will continue to increase in fiscal year 1964.

IDENTIFYING THE CAUSES

Less than 10 years ago, estimates in the literature ranged widely concerning the role of obstetrical factors and perinatal events in the etiology of cerebral palsy. Birth processes were estimated by some investigators to contribute to only 5 percent of cases of brain damaged children, while others suggested that 50 percent of the cases could be traced to these processes. While the relationship of perinatal complications and cerebral palsy is now being clarified, the medical literature still presents restatements of the old question: to what extent are prematurity, asphyxia and other birth difficulties the result rather than the cause of the central nervous lesions underlying the cerebral palsies?

In a retrospective study supported by the National Institute of Neurological Diseases and Blindness and the United Cerebral Palsy voluntary organization, investigators looked intensively into the history of 753 children afflicted with cerebral palsy and made comparisons with an equal number of normal children.

It was found that more than half of the babies born with spastic paraplegia (a common form of cerebral palsy in which both legs have tense, contracted muscles) had been born prematurely. When the various forms of cerebral palsy were considered, 31.2 percent had been born prematurely, compared with only 8.2 percent in the control group. The findings in the study of the 753 palsied children were quite clear cut. In about 55 percent of the cases, causative factor could be deduced from the records. These included complications of labor and of pregnancy, kernicterus or jaundice of the newborn, certain acute infectious diseases, and head injuries.

While much research remains to be done on the etiology of cerebral palsy, progress is evident in diagnosis, treatment, and prevention of this condition.

ACCOMPLISHMENTS OF THE PAST YEAR

Diagnosis sharpened

The great majority of cerebral palsy cases are not recognized with certainty until the infant is 6 months of age or older. However, the clinician's ability to recognize the child with brain damage up to the age of 1 year is being sharpened through the diagnostic experience of the Institute' collaborative project. Approximately 8,000 infants were born during the past year to the 40,942 study mothers participating in this project, bringing the total to 33,325 infants.

It once was said that a physician delivering 100 babies in a year really delivered "5 babies 20 times" so conventional and time honored was the process. With the introduction of methods of detailed recording at time of birth and thereafter (the study protocol), physicians have become increasingly aware of the details of labor and delivery to be recorded. The syndrome of cerebral palsy is being more readily recognized and the diagnosis substantiated by methods which permit simultaneous exploration of several hundred characteristics of pregnancy and the pregnant woman.

Rubella susceptibility indicated

Virologists associated with the collaborative project have participated in recent research which has characterized the virus of German measles (rubella). This virus is a cause of congenitally malformed infants, including those with cerebral palsy, when the infection is acquired by the mother during the first 3 months of pregnancy. Investigators of the National Institute of Neurological Diseases and Blindness have worked with those of the National Institute of Allergy and Infectious Diseases in the research which has provided means for assaying antibodies against the rubella virus. Preliminary studies reported last year have shown that nearly one in five women of childbearing age have virtually no antibody protection against rubella infection. This work also has pointed to the need for consistently higher concentrations of these antibodies in gamma globulin administered to pregnant women who have been exposed to the infection. The groundwork has been laid for a protective vaccine against rubella and there is reason to be optimistic that this vaccine will be developed in the near future. When proven safe and effective, it would be particularly useful to women of childbearing age by preventing infection and consequent damage to the fetus.

Toxoplasmosis

Toxoplasmosis, a protozoan infection acquired prenatally from the mother or at any time postnatally, may lead to death of the fetus or to residual manifestations such as cerebral palsy. Institutions of the collaborative project have provided 27,000 sera samples from which titers of antibody to toxoplasmosis are being determined. Initial data shows that 2½ percent of study mothers have moderate to high titers, indicating infections that may have occurred relatively recently, possibly during the study pregnancy. These findings provide a method for retrospective examination of pregnancy outcome as related to toxoplasma infection.

Asphyxia

Another of the varied factors which may contribute to cerebral palsy is asphyxia, or lack of oxygen just prior to or at the time of birth. The Institute's Laboratory of Perinatal Physiology in Puerto Rico has ben studying pregnancy and labor in newborn monkeys, seeking analogies to human processes. Here it has been observed that asphyxia sets off a delayed chain reaction. The delayed effect includes a swelling of the brain substance and a resultant interference with the circulation of blood. The intravenous administration of glucose and alkali has been found to modify the damage from asphyxia in the experimental studies in Puerto Rico.

Prevention of kernicterus

Kernicterus or jaundice of the newborn is a cerebral palsy related condition. One of the important causes of kernicterus is blood incompatibility. A recent grant-supported study of cerebral palsy families conducted by the College of Medicine, University of Utah, reported that the most significant finding was the number of Rh incompatible families. In a group of 27, there were 17 with a demonstrable Rh immune titer in the maternal serum. The report concludes that the significance of the Rh antibodies and the development of kernicterus would appear to be an important factor in the etiology of the cerebral palsied child in the Rh incompatible families.

In a pilot survey of several hundred babies in the collaborative project, nearly 2 percent were found to have evidence of Rh blood incompatibility. Exchange blood transfusions given to remedy this undoubtedly saved scores of infants from kernicterus and resultant brain damage.

EMPHASIS ON PREVENTION

Good clinical practice is being encouraged by the emphasis on prevention. For example, hypoglycemia, or low blood sugar, may be alleviated by diet before it causes cerebral palsy. Severe diarrhea in infants, which may leave them so dehydrated that brain damage results, can be modified by better care. Recently investigators elsewhere have shown a correlation between prematurity and maternal subclinical urinary tract infection (with bacterial counts in excess of 100,000 in 1 milliliter of urine). A simple test is available to detect bacteriuria in the prenatal period. Through a large-scale study, it should be possible to further verify this correlation and determine whether treatment of significant bacteriuria in the mother might prevent some cases of cerebral palsy and other abnormalities in the child.

The data now being processed in the NINDB's Perinatal Research Branch, should point to damage that can be prevented. For example, heavy smoking by pregnant women has been correlated with low birthweights of their infants in a preliminary survey. The full-scale study of this phenomenon is continuing. Indeed, it might be said that "premature" mothers also contribute to cerebral palsy, for it has been found through studies elsewhere in the Institute that mothers aged 14 or less experience a high percentage of birth difficulties.

THE SEARCH FOR CLUES

Research is continuing to differentiate between the various forms of cerebral palsy and to find clues that point to the mechanisms involved. Institute grantees in Detroit and Seattle collaborated in a recent report on 5-year studies which point to respiratory distress at birth as a more important factor in one form of athetoid cerebral palsy than had previously been recognized. (Athetoid refers to the constant, uncontrolled motions of limbs characteristic of this type.) One of these grantees further pointed out an association between neonatal weight loss in premature infants and spastic diplegia. The weight losses were greater in the cerebral palsied prematures than in comparable prematures without this condition. From such patient-centered studies eventually will come a much clearer picture of the mechanisms of cerebral palsy.

At the moment, no such method for restoration of damaged brain tissue exists. More precise knowledge of the normal mechanism of the brain will be required Many studies have shown that the growth of the nervous system and the orderly distribution of its component structures depend upon a very complicated chemical interplay. Brain growth could be modified, increased, or reduced by modifying the chemical interaction of the structures as they develop. A precise knowledge of the various stimuli which cause tissue growth will be required in order to influence the regrowth of cells and other structures in the injured brain.

In the search for clues to the mechanisms of cerebral palsy, basic laboratory research offers promise of broad progress. New electronic methods are constantly extending the senses of investigators, as computers examine the activities of constellations of the brain cells among the billions to be studied, and microelectrodes take the electrical potential of a single cell among these billions.

Pathology

In the collaborative project, brain specimens collected by many medical centers from terminal cases of cerebral palsy are being studied in attempts to correlate the clinical observations with observed brain lesions. The project cooperates with the Academy of Cerebral Palsy in maintaining this brain registry. In Puerto Rico, the Laboratory of Perinatal Physiology is conducting similar studies of lesions in the brains of infant monkeys with a condition much resembling human cerebral palsy.

SUMMARY

Although cerebral palsy eventually may be defined precisely in terms of specific brain lesions and faulty electrochemical-pathways of nerve activation, its manifestations will remain varied and complex.

The spastic, the athetoid, the rigid, the ataxic (poor balance), and the tremorous, all are types of cerebral palsy. The spastic type is most common. Patients with this type often are classified according to the number of limbs involved (quadriplegia, tetraplegia), or only one side of the body (hemiplegia) or rarely, only one limb (monoplegia).

Almost any combination of physical and mental states is possible. The brain damage may be sufficiently extensive to cause mental retardation. A considerable proportion of the mentally retarded also show other manifestations of cerebral palsy; but many cerebral-palsied individuals have no mental incapacity. Some of the cerebral palsied have partial or complete deafness. Some have limited eyesight. Many speak with difficulty, or not at all. Those who have poor control of themselves may be under constant emotional strain, but, like other handicapped individuals, some make a strong adjustment to self, family, and society.

To find solutions to the many unanswered problems presented by this disease, the Institute has brought substantial resources to bear. Contributions to knowledge are coming from research by its laboratories in Bethesda; from surgical and electrographical studies in the new neurosurgical suites of the surgical wing, clinical center; from the collaborative project; from the Laboratory of Perinatal Physiology in Puerto Rico; and from grant-supported centers throughout the Nation. Thus, the National Institute of Neurological Diseases and Blindness continues to place major emphasis on finding means to prevent or diagnose and treat cerebral palsy.

GERMAN MEASLES

Dr. MASLAND. We are working on the German measles virus. We have found that, within our population of pregnant women, about 17 percent are susceptible to German measles who have not had this disease. We also find that many people do not know whether or not they have had it. It is such a mild disease, and so easily confused with other things, that a woman's report as to whether or not she has had German measles is unreliable.

We have been able to verify this now because, since the virus has been isolated, we have a specific antibody test for German measles. We can determine definitely who is susceptible and who is not.

Mr. FOGARTY. Is this vaccine working out all right?

Dr. MASLAND. We have tested, in a small group of volunteers, a killed-virus vaccine, which provided immunity. There is uncertainty as to whether a killed-virus will be adequate or whether we will have to develop a live virus.

Mr. FOGARTY. Is this the one that was worked on by John Enders?

Dr. MASLAND. That was the regular measles virus. An associate of Dr. Enders, Dr. Weller, is also working on the German measles virus. Dr. Busher, at the Walter Reed has been working on it, and Dr. Sever in our Institute. They are making very rapid progress.

The other thing that they have is an immune serum, or gamma globulin and until such time as the vaccine is available, probably the gamma globulin does provide some protection for a woman who has been exposed during pregnancy. It is a very important concern because of the injury of the fetus and the congenital malformations which often occur.

Mr. FOGARTY. This is one of the things that causes cerebral palsy?

Dr. MASLAND. That is right.

DRUG TREATMENT OF CEREBRAL PALSY

Mr. FOGARTY. Is there anything else you want to report?

What about this new drug for victims of cerebral palsy?

Dr. MASLAND. Yes. There is a drug called diazopam. This is a drug which is somewhat related to some of the tranquilizing drugs. It was first given to patients with cerebral palsy in the hope that it would make them less nervous and difficult to handle.

Cerebral-palsied children who are frustrated are likely to be difficult, and it was thought that a tranquilizer would be helpful. It was discovered that this drug is even more effective than that. In the individual who is athetoid, who suffers from involuntary movements, there is an actual reduction in the spasm and in the involuntary movement, with a resulting improvement of voluntary movement. It looks as if this drug would have a really valuable role in the handling of those children.

MENTAL RETARDATION

Mr. FOGARTY. Are you in agreement with Dr. Felix and Dr. Aldrich on your approach to the problem of mental retardation?

Do you have any problems between Institutes and with the Children's Bureau?

Dr. MASLAND. We have a committee in the Institute, among the Institute Directors and staff.

Mr. FOGARTY. Dr. Whedon told us something of interest this morning about newborn children with jaundice, that might be retarded later on. Something can be done now by taking the child off the mother's milk. That is something new in the last year, isn't it?

Dr. MASLAND. Yes. I might also mention something which is developing very well, and this is the test of Dr. Guthrie for phenylketonuria. Dr. Guthrie originally started his work on that as an ancillary of the collaborative project; then he was provided with an independent grant, and as you know, 2 or 3 years ago, developed a method making possible the early recognition of phenylketonuria.

The Children's Bureau has supported a large screening test in Massachusetts, using this method which he developed, and I understand that 40 children with phenylketonuria have already been detected.

Mr. FOGARTY. I think all the hospitals in Rhode Island are about to institute this detection technique.

This is working out fairly successfully?

Dr. MASLAND. Very well.

Mr. FOGARTY. They have to be examined after they leave the hospital, 3 or 4 months later; do they not?

Dr. MASLAND. The advantage of Dr. Guthrie's test is that it will detect most instances of this disease as early as 24 hours after the child has had its first meal of milk. That usually is about the third day. It means that in those hospitals where the babies are not sent home prior to the third day the test can be used in the hospital. This is a tremendous advantage because it can be made a routine part of the delivery process. Once the baby has gone home it is much harder to be certain that the other tests are going to be made.

Mr. FOGARTY. So another test does not have to be done later?

Dr. MASLAND. Not if this test can be made. Now, as part of the evaluation of this test and in order to find out whether it is, in fact, missing any of these children, a followup study is being made at the age of 3 or 4 months using the standard urine test. My impression is that this test is picking up these children very well.

(Following is a special report on mental retardation submitted at the request of the committee:)

SPECIAL REPORT: MENTAL RETARDATION

THE ROLE OF NINDB

The role of the National Institute of Neurological Diseases and Blindness in mental retardation research relates to the Institute's responsibility to conduct research on those biological factors which cause injury or dysfunction of the brain and nervous system. Many of these factors result in mental retardation.

Since its founding in 1950, the Institute has moved steadily forward in its investigation of injurious factors causing brain damage both at its Bethesda laboratories and through supported research projects at many medical centers. In addition to this research, two extensive programs which have been of particular interest to those studying mental retardation are the Institute's collaborative perinatal program and its research program at the Laboratory of Perinatal Physiology in Puerto Rico.

Soon after the Institute was established, it launched a revolutionary attack against the early factors causing damage to the nervous system. The long-term collaborative project is studying 50,000 mothers and babies from early pregnancy, through labor and delivery, and until the children are 7 years of age. After extensive preparation, the main phase of the study began in 1959 and is being carried out at 15 collaborating medical centers throughout the Nation.

The objective of the study is to help discover the factors operating in the perinatal period or early childhood which damage or inhibit the development of normally functioning neurological and sensory systems. Attempts are being made to relate the observed deficits in project children to the circumstances and events of pregnancy which may have been responsible. Previous studies had considered many of these factors retrospectively, but the Institute's program is the first to study a large number of cases prospectively.

Valuable information has already been obtained concerning the causes of prematurity, neonatal asphyxia and jaundice, and the impact of these conditions upon the child's developing nervous system.

In addition to specific research findings from the project, of particular significance to future research in mental retardation is the multidisciplinary approach to the problem of brain damage which is now being used at the 15 collaborating medical centers. When the project was started, few obstetricians were occupied with perinatal research, there was little research liaison between the obstetrician and the pediatrician, the number of pediatric neurologists was small, and most neurologists were occupied with adult neurology. An indication of the cooperation which has developed is seen in the statement of a leading obstetrician who said of the project: "It has brought the pediatrician to the delivery room and taken the obstetrician to the nursery."

For the past 7 years, scientists at the Institute's Laboratory of Perinatal Physiology in San Juan, P.R., have been studying in monkeys many harmful factors, particularly asphyxia, which produce injury to the newborn. They have found that infant monkeys asphyxiated and resuscitated at birth develop varying degrees of symptoms similar to cerebral palsy and mental detardation. Recent research has provided clues to the prevention of such damage.

TRAINING PROGRAMS

At the time of the establishment of the Institute, there was a critical shortage of trained neurological scientists to provide special care and conduct research on disorders of the nervous and sensory systems. Many States were without a single neurologist, and in only 15 medical schools were there approved specialty training programs. In order to expand the training effort, it was necessary for the Institute first to concentrate on the training of specialists for teaching and research. Today there are over 120 training programs in the neurological sciences. In a decade the numbers in training in clinical neurology have jumped from 90 to over 400, and the total trainees in the neurological sciences are over 600. Over these years, the Institute has provided support for approximately 900 postdoctoral and special fellows, and, through its graduate training grants, has contributed to the training, environment, and personal support of an estimated 1,600 specialists.

In 1957 the Institute launched a new program to train neurologists to specialize in neurological disorders of infancy and childhood. There are now 11 such programs, and over 40 men are receiving this training in order to become leaders of the new and broadened attack on these disorders.

These men cannot begin to meet the needs for day-to-day medical care for the mentally retarded. They can, however, provide essential training and consultation services to the many physicians of other disciplines who must be involved in the newly developing national program.

SCIENTIFIC ADVANCES

Collaborative project accomplishments

Studies of the collaborative project have produced results of wide interest to scientists working in the field of perinatal biology, both as confirmations of observations made in clinical practice and as sources of new information in areas in which little material has been available to researchers.

A substantially increased risk has been demonstrated with the young and older mother regarding perinatal mortality, prematurity, and congenital malformations. It has been demonstrated that women, whose last prior pregnancy ended in a liveborn child weighing less than 4.4 pounds, have a prematurity rate of 36 percent in the subsequent pregnancy. Conversely, if the last prior child weighed in excess of 7½ pounds, the prematurity rate in this pregnancy drops to around 3½ percent.

The study of the placenta has revealed many interesting findings which appear to be related to abnormal pregnancy outcome. Thus, umbilical artery aplasia was reexamined with project data confirming that this condition occurs frequently in association with other congenital anomalies and is related to an increase in preinatal mortality.

Inflammation of various placental tissues is a relatively frequent event. Its association with prolonged labor, fetal and neonatal deaths, and its almost complete absence in elective cesarean section seem to suggest that infection may be the crucial factor. In addition, a gross disparity between placental and birth weights identifies groups of children with a high perinatal mortality rate. This is particularly apparent when the placental weight is disproportionately small for a given birth weight or length of pregnancy.

Many studies are seeking to identify characteristics of newborn children which may forecast an increase in neonatal mortality rate or neurological abnormality rate in surviving children. To date, the Apgar method of assessment of the newborn child, both at 1 and 5 minutes, appears by far to be the best predictor. The 5-minute Apgar rating seems to be much more strongly associated with neonatal mortality and neurological morbidity at the 1-year level than the 1-minute Apgar rating.

A marked increase in neurological abnormalities has been observed in premature children. Thirty percent of neurologically abnormal children at 1 year of age are prematures, while only 10 percent of all births are prematures. About 10 percent of all neurologically abnormal children at 1 year show signs of asphyxia in the immediate neonatal period. With project data, the importance of asphyxialike states can be evaluated.

A reinvestigation of the problem of hyperbilirubinemia of prematurity and its importance in brain damage is now in progress. Investigators are questioning the standards currently being applied in bilirubin testing and are suggesting that lower levels of danger should be established.

In an extensive serological investigation of perinatal infections, 36 percent of 25,000 pregnant women showed serological evidence of prior infection with toxoplasmosis, and 2½ percent indicated recent infection. Seventeen percent were found susceptible to German measles. Over 10 percent experienced some viral infection during pregnancy.

For the study of virus infections during pregnancy, specimen collections are being expanded to include tissue samples from placentas, abortuses, stillbirths, and neonatal deaths in order that isolated viral agents may be utilized to confirm and extend the serological findings. Investigations will be conducted with experimentally infected pregnant and nonpregnant animals to provide direct information on routes of infection, pathogenesis, and possible methods of prevention of defects in the fetus due to infectious agents.

Preliminary studies with the injection of an inactivated rubella antigen suggests that protective effects may occur. Further studies on inactivated and attenuated vaccines for rubella are being pursued by laboratory and clinical approaches.

To evaluate the effects of drugs during pregnancy, data from study pregnancies are available and are being supplemented by data from other sources. These and many other individual analyses are now making broad contributions to our knowledge of the many perinatal factors in the neurological and sensory disorders of infancy and childhood.

Early diagnosis

In addition to accomplishments under the collaborative project, Institute grantees in Denmark this year developed a chemical method for diagnosing several rare disorders causing mental retardation. The method combines paper electrophoresis and infrared analysis to identify an acid mucopolysaccharide found in urine in persons with Morquio-Ullrich's disease and gargoylism.

In a limited study this year, Institute grantees observed an abnormally high content of specific acids, homovanillic and/or vanilmandelic, in the urine of patients with brain tumors. These preliminary findings may provide an effective method for the diagnosis of brain tumors, such as neuroblastoma, which often cause mental retardation.

A new technique for the early mass screening of phenylketonuria (**PKU**) has been designed by Institute grantees. This has been important in diagnosing the disorder and gaging the effectiveness of the necessary special diet for the newborn before it leaves the hospital. The diet has done much to prevent mental retardation previously associated with PKU and Hartnup's disease.

Also to aid in the very early recognition of infantile cerebral palsy, investigators now recommend that additional reactions be incorporated in the examination. These include tonic-neck, labyrinthine and righting reflexes, positive supporting and contact placing reactions, the traction response, the avoiding response, and the grasp reflex for identifying the condition and understanding the motor disorder.

Genetic studies

Many forms of mental retardation are attributable to genetic factors or to specifically inheritable brain defects. Recent advances in our knowledge of the structure of the gene and its mechanism of action are making possible a precise knowledge of the biochemical defects which underlie these important and serious forms of mental retardation. This knowledge leads to precision in diagnosis, to the development of specific means of prevention and cure in some instances, and, in others, to the recognition of carrier states whereby individuals likely to have defective offspring can be recognized and provided with the benefits of enlightened genetic counseling.

For example, this year, new evidence regarding the chemical defect in the genetic disorder called Wilson's disease has been developed. In this disorder, it has been known that an abnormal accumulation of copper exists in certain nuclei of the brain. It has been clear that the presence of copper in these areas is regularly accompanied by structural and functional alterations leading to the devastation of this disease. Nevertheless, the biochemical action of copper within these tissues has been obscure. Recent efforts indicate that the copper acts largely within the mitochondria, where it manifests two antithetic, or opposing, biochemical reactions. In one, it acts to split the nuclease known as flavine adenine dinucleotide. In the other, succinate blocks the action of copper to any other substance by combining with it in a process called chelation. The observation of these specific biochemical reactions of copper in the cell is an important step toward the development of specific biochemical means of obviating this toxic effect.

In the study of Tay-Sachs' disease, another inherited neurological disorder causing mental retardation and uniformly fatal, Institute grantees have recently discovered a method for the identification of carriers of the gene of this disease. Studies have demonstrated the occurrence in the bloodstream of affected individuals of a specific enzyme deficit in more than 600 persons tested. This enzyme deficit has been found in persons with the disorder and in their relatives who do not have the disease, but are carriers of the gene. When two such individuals are married there is a probability of Tay-Sachs' disease occurring in one out of four of their children. The enzyme deficiency, and thus the carriers of the disease, can be detected by a relatively simple chemical method. A central registry has been established for the disorder, and physicians across the country are contributing information.

Additional information relating to Tay-Sachs' disease has come from Institute investigators in Israel who have isolated two new glycolipides from brain tissues of patients with the disorder. These two studies are throwing new light on the essential nature of the disorder.

Damage from asphyxia of the newborn

There have been literally hundreds of speculative commentaries on the concept that mental retardation is related to anoxia or asphyxia during or immediately subsequent to birth. However, few controlled human studies and even fewer animal experiments have been carried out to establish the relationship, determine the extent of permanent damage, and provide a scientific basis upon which to institute methods of prevention and therapy. Within its Bethesda laboratories, through research grants to outstanding investigators around the world, and especially through the Institute's Laboratory of Perinatal Physiology in Puerto Rico specifically developed to attack this problem, the Institute has mounted a major effort to attack this problem.

It is evident that the brain damage resulting from asphyxia may be the result of many mechanisms. Recent studies by a grantee in England indicate that intracellular acidosis is a major mechanism. The studies indicated that the immediate cause of all the brain damage is intracellular acidosis or lowered blood bicarbonate, caused by impaired circulation in the capillaries. Specific patterns of brain damage were associated with specific types of circulatory deficiency. One type causes damage to the gray matter of the brain and the areas near the large arteries, another damages the white matter, and another causes edema of the white matter which, in turn, may cause secondary lesions to the blood vessels themselves.

Scientists have discovered recently that the administration of an alkali-glucose mixture to the fetus helps to counteract the cellular acidosis and to minimize damage from asphyxia at birth. In the Laboratory of Perinatal Physiology in Puerto Rico this mechanism has been subjected to an intensive investigation. This method of treatment was administered to a large series of asphyxiated animals in order to evaluate its beneficial effects and to study its mechanism of action. Pathological examination of the brains of treated and untreated asphyxiated animals reveal a striking reduction in the extent of the brain damage experienced by the glucose-alkali treated animals. Even when this treatment was administered to the mature fetus late in asphyxia, when the circulation had begun to fail, it facilitated resuscitation and accelerated recovery.

In other experiments, a combination of asphyxia plus induced hyperbilirubinemia in infant monkeys resulted in a condition clinically and neuropathologically resembling kernicterus as seen in the human. This technique, for the first time, provides an experimental model for the study of this common cause of mental retardation and cerebral palsy.

Effects of radiation

In current studies, special attention is being given to the effects of X-irradiation on the fetus when used in examination or treatment of the pregnant woman. Investigators have shown in animal studies that even a single low dose of X-irradiation can cause permanent damage to the highly sensitive central nervous system. The type of damage is closely related to the time of exposure, but damage may be caused at any time from fertilization of the egg to the completion of development after birth. The damage may not appear immediately and attention is now being directed on long-term and genetic effects.

Toxic effects of chemicals

The effect of chemical substances on the brain and other parts of the nervous system is receiving increased attention, especially since the thalidomide experience. Recent animal studies have shown that tetracycline, a widely used antibiotic, may inhibit growth, reduce expected fetal size, and cause prematurity, but the significance for humans is uncertain.

Lead poisoning is not an infrequent cause of mental retardation. It occurs in children 1 to 3 years of age, and is usually caused by eating lead paint. Recent investigations have indicated that the essential process bears many resemblances to changes associated with asphyxia—a major factor in the pathogenesis of lead toxicity being changes in the permeability of the blood vessels of the brain. Here again the major cause of brain damage appears to be the swelling and compression of the brain which results. A broad-scale investigation of this mechanism of brain edema is an important part of the Institute's developing program.

Viruses

Institute grantees this year confirmed the suspected association between aseptic meningitis, a cause of mental retardation, and ECHO 20 virus by isolating the virus from the cerebrospinal fluid of an affected patient. ECHO 20 is a virus previously isolated from infants and children with mild respiratory-intestinal disease.

CONCLUSION

These advances represent but a few areas of the Institute's broad program for the investigation of the nervous system and its disorders. Such knowledge is the essential basis upon which can be built a broad program for the prevention and treatment of mental retardation.

PARKINSON'S DISEASE

Mr. Fogarty. What about Parkinson's disease? It seems to me I see more people with this disease now than ever before. Is it on the increase, or do you know?

Dr. Masland. We do not know for certain. We are now developing a program to find out whether it is increasing or decreasing. A certain number of cases of Parkinsonism are the result of encephalitis. There was a very serious epidemic of encephalitis right after the influenza epidemic in 1918–20. Many cases of Parkinsonism resulted and there has been one school of thought which suggested that all Parkinsonism was due to this cause. However, we have gone back into the records before that epidemic and we know there was plenty of Parkinsonism before. Also, we do not find any falling off in Parkinsonism now, and we believe there is a lot of Parkinsonism due to causes other than infection.

One of the most important activities of the Institute this past year has been the establishment of a Parkinsonism Center in New York. This Center differs from our other research centers in that, in addition to a broad general program of research, we are asking the Parkinsonism Center to develop an information center and a program analysis function. They will do this under a contract. It will be their responsibility to maintain a continuing surveillance of this field of the Institute's responsibility, in order to advise us on opportunities and needs in this area.

Mr. Fogarty. Isn't there anything you can give a person now that will help the tremor?

Dr. Masland. There are two methods of treating Parkinsonism. There is a surgical approach which is valuable in selected cases, particularly those who have predominantly tremor. The trouble is that the individual with Parkinsonism suffers from a triad of symptoms: tremor, rigidity, and a loss of normal balancing movements.

He loses the automatic movements we all make when we walk instinctively.

Now, the surgical procedure is, after all, a destructive procedure. It does not put in something that is not there; and although it relieves the tremor in some cases, it has very little beneficial effect on the rigidity or, more particularly, this loss of movement.

The second method——

Mr. Fogarty. How does it affect a person as far as rigidity is concerned? Do they just stiffen up?

Dr. Masland. They just become very stiff.

Mr. Fogarty. Sitting down, or in bed, or walking?

Dr. Masland. All the time, except when they are asleep. When they go to sleep they relax.

Mr. Fogarty. How do they walk? Can they walk?

Dr. Masland. They walk very slowly and stiffly. Of course, there are varying degrees of Parkinsonism, and the rate of progress is variable. Some individuals have minor degrees of Parkinsonism for many years.

The hopeful approach to Parkinsonism is through drugs. It is now quite clear that Parkinsonism results from an imbalance between two of the control systems in the brain. There is a balance between these two, and if one is weakened, the overactivity of the other causes the tremor and stiffness.

By giving drugs which enhance one or inhibit the other, you can alter this balance. One of the important contributions to this knowledge came from observing the side effect of certain tranquilizers. Some of the tranquilizing drugs, if given in large doses, actually produce Parkinsonism. It has been discovered that those tranquilizers block the chemical factors in one of these systems. This makes us suspicious that in the disease itself there may be a similar process going on; that there is a toxic agent or some other mechanism which has poisoned that system, and that if we can find out what that is, we ought to have a real key to this disease. This will be one of the major focal points of the Columbia project. A report I have here tells of this in more detail.

Mr. FOGARTY. We will put it in the record.

You can live for many years with this disease?

Dr. MASLAND. That is right. Most neurological diseases are disabling and crippling, rather than killing. In this connection, we find that the death statistics are very badly distorted for this reason. An individual who has Parkinsonism develops pneumonia as a terminal event, and dies of pneumonia, and on the death certificate it is indicated as a death from pneumonia. Parkinsonism does not appear on the record. We know from studies that there are about three times as many individuals who die with Parkinsonism as show up on death certificates as dying of Parkinsonism.

Mr. FOGARTY. Well, we are attempting to get better health statistics now, are we not; and better reporting systems in the States?

Dr. MASLAND. This is one of the things we are working on.

(The special report referred to follows:)

SPECIAL REPORT ON PARKINSONISM

THE PROBLEM

The name "Parkinsonism" applies to a combination of symptoms, including tremors of hand and foot, rigidity of muscles, slowness of speech, and disturbances of posture and gait. These symptoms result from a disease process with a selective action upon certain structures deep within the brain. Parkinsonism applies to several related conditions in which tremor, muscle rigidity, and alteration in walking are key symptoms. As in certain other neurological ailments. Parkinsonism thus covers a group of medical entities, undoubtedly with different causes.

An estimated 25,000 to 43,000 persons are newly afflicted each year. Parkinsonism is a chronic ailment which often lasts from 10 to 40 years, and rarely kills its victims directly. The accumulated prevalence is now estimated at 300,000 to 500,000 in the United States.

Two opposing viewpoints on the future magnitude of the problem led to a recent editorial (November 23, 1963) in the Journal of the American Medical Association. The view of scientists at the Institute and many other investigators has been that, because Parkinsonism is primarily a problem of those 40 years and older, and because both the total and the relative number of the over-40 age group is increasing in the United States, Parkinsonism can be expected to increase until a preventive and a cure are found.

The opposite view proposes that much of the Parkinson's disease is postencephalitic, a sequel of the epidemic of encephalitis lethargica (Economo's disease) which ran its course from 1916 to about 1930, during the time of the great influenza pandemic of 1919 (1918–25). Because serological diagnosis was less precise at that time, a patient's history of "flu" has often been deemed presumptive evidence of postencephalitic Parkinsonism. If this is valid, then the number of patients with Parkinsonism can be expected to drop sharply as the lifespan of survivors of the "flu" epidemic terminates.

On the contrary, the Journal editorial reaffirms the Institute view, citing the prevalence of classical Parkinson's disease before the 1918–25 epidemics, and stating that the proportion of postencephalitic cases is now quite small. From this, the editors conclude, "Parkinsonism is hardly on the wane and will continue to be a major neurological problem for many years to come. A continual and vigorous attack on this disease to find the cause and means of prevention, is as important as ever."

INFORMATION ON CAUSES

A few specific causes of this ailment have long been recognized or strongly suspected. In addition to postencephalitic Parkinsonism, a few specific cases result from poisoning, such as by carbon monoxide or manganese. But in the great bulk of the cases in the United States, causation remains a major research problem.

MEDICAL RESEARCH

Medical research on Parkinsonism involves several approaches. Present medicinal therapy provides only partial symptomatic relief, and untoward side effects or developing tolerance or intolerance require frequent revisions by the physician or the medication program for the individual patient.

Recent discoveries are clarifying the mechanism of action of drugs which have long been used empirically for the relief of Parkinsonism. Tremor and muscle rigidity in this disease result from an imbalance between two interacting motor-control systems within the brain. Injury of one system by the disease leads to relative overactivity of the other. By stimulating one system, or inhibiting the other, drugs can restore a more normal balance. Research is attempting to discover naturally occurring enzyme systems which may be distorded by the disease process and thus lead to impairment of these motor systems. Accurate knowledge of the neurochemistry of the brain, and especially of the normal chemical components of these two motor systems, is required.

PROGRESS IN SURGICAL RELIEF

Another method for restoring proper balance in these motor systems is by surgical destruction of the overactive pathway. Both at the Institute and elsewhere refinements continue in surgical relief of symptoms by stereotactic brain surgery. Among techniques of producing a tiny brain lesion in the thalamus of the brain, cutting, electrocoagulation injection of alcohol or other chemicals, freezing, and ultrasonics have successfully relieved tremor and rigidity but not postural complications in many patients. The surgery can be used only in carefully selected cases; the relief has not always been permanent. For these reasons, research for improvements in surgical techniques continues, as well as a search for a preventive and for a successful medical treatment.

A SECOND SYMPOSIUM ON PARKINSON'S DISEASE

A second symposium on Parkinson's disease, held in November 1963, under the auspices of the Veterans' Administration, stressed the broad scope of the research program on Parkinsonism. Special emphasis was put on the role of metabolic studies. A newly identified substance in the urine, called PR for Parkinson's disease, was reported as a possible important link in the biochemistry of the disease. In further neurochemical research, the significance of adrenalin, noradrenalin, and acetylcholine as precusors or transmitters was suggested for more study on the physiology of this disease. Additional experimental investigation was requested on the effects of chronic manganese poisoning which resemble Parkinsonism.

RESEARCH ON PARKINSONISM ON GUAM

For the past few years the Institute has conducted an active investigation of a native population with an incredibly high frequency of Parkinsonism on the island of Guam. The most recent figures indicate that 7 percent of this population are afflicted with a severe form of rapidly progessive Parkinsonism—in this instance associated with dementia.

An intensive field investigation of this unique situation is now underway. Pathological examinations of the brains of patients who died from this disease are being conducted. Epidemiological studies are attempting to find environmental factors which may be influencing the incidence in the population on Guam.

BASIC STUDY WITH ELECTRONIC DEVICES

New knowledge in the anatomy and physiology of Parkinsonism is coming from electrical and microelectrode research on areas of the brain involved in Parkinsonian activity. These have practical value in the placement of the surgical lesions which relieve some symptoms, and theoretical value in the continuing search for a cause of this distressing disease.

INTENSIVE RESEARCH CENTER ESTABLISHED

It is apparent that anatomical, biochemical, and physiological advances are being made and that the time is now ripe to launch a more coordinated and intensive attack against Parkinsonism.

A new Parkinson's disease study center at Columbia University, recently established and supported by the Institute, provides a multidisciplinary approach which could become a prototype for categorical investigations. In its research area, the study center will conduct a comprehensive research program directed toward determining causes, improving diagnostic techniques, and developing methods of treatment and management of Parkinsonism and related movement disorders.

In its information area, integrated with the research center, the latest scientific information regarding Parkinsonism and related disorders will be collected, reviewed, and disseminated. Its activities will make it a reference center for investigators and a source where physicians can be advised of current therapy. This should help to shorten the lag between scientific progress and everyday medical practice.

SPECIAL REPORTS ON MUSCULAR DYSTROPHY, MULTIPLE SCLEROSIS, AND EPILEPSY

Mr. **Fogarty**. What about the muscular dystrophy? Do you have anything special? We put your prepared statement in the record.

Dr. **Masland**. Yes. We have a special report for the record, too, on muscular dystrophy. Our approach to muscular dystrophy still emphasizes the recognition of the basic nature of the disease. We do not have a treatment for muscular dystrophy which is proven, at this time.

Mr. **Fogarty**. You do not have one for multiple sclerosis, either.

Dr. **Masland**. No.

Mr. **Fogarty**. Do you have a special report on multiple sclerosis?

Dr. **Masland**. Yes.

Mr. **Forarty**. What about epilepsy?

Dr. **Masland**. Yes, I have a special report.

Mr. **Fogarty**. Put them in the record.

(The special reports of muscular dystrophy, multiple sclerosis, and epilepsy are as follows:)

Special Report: Muscular Dystrophy and Other Diseases of Muscle

MULTIPLE PROBLEMS

Intensive research in recent years has demonstrated that muscular dystrophy is not a single entity but represents a group of ailments called the muscular dystrophies. They belong to a still larger group of neurologic disorders called neuromuscular disorders.

Included in the neuromuscular category are not only muscular dystrophy with estimates running as high as 200,000 patients, but also myasthenia gravis, affecting 30,000 patients, and periodic paralysis affecting an undetermined number of patients.

The economic, social, and personal problems of the neuromuscular diseases vary with the entity. Muscular dystrophy most often affects children and young adults, is generally hereditary, and at present incurable. The condition is characterized by progressive weakness and wasting of the muscles, typically leading to paralysis, deformity, and often incapacity.

Other neuromuscular ailments have onsets in infancy, in youth, or in adulthood. Their duration ranges from a rapid downhill course with an early fatal termination to a slowly progressive, chronic disorder lasting throughout a normal lifetime.

From its inception, the Institute has used every research method and every research discipline which offered hope for conquest of the neuromuscular disorders. This multidisciplinary research approach involves neurochemists, neurophysicists, neurophysiologists, neuroanatomists, and geneticists, as well as clinical neurologists.

While the common denominator of the muscular dystrophies is the loss of muscle tissue, recent studies have shown that there are several types with different characteristics. In past years scientists at the Institute have identified some of these disease entities which were previously grouped under the general category of muscular dystrophy. For this purpose, they have been using the modern techniques of clinical biochemistry, clinical physiology, immunology, histochemistry, biochemistry, electron microscopy, and tissue culture.

In all these studies, the objective is to determine with accuracy the essential nature of the structural or biochemical defect of this disease. Muscular dystrophy, like the inborn errors of metabolism such as phenylketonuria, appears to depend upon a specific enzyme defect. The precise identification of this defect is an essential step on the pathway toward cure of muscular dystrophy.

DIFFERENTIATION OF TYPES

Among specific varieties of muscular dystrophy have been found two with distinct and different enzyme defects. Another variation produces a characteristic abnormality of the muscle with a recognizable "central core" of atypical tissue within the muscle fiber. Still another newly defined syndrome of muscle weakness produces symptoms of mental retardation and obesity, as well as flaccid muscles. The responsible metabolic cause has not yet been pinpointed.

Progress in research on myasthenia gravis also has led to differentiation of types. Certain cases with considerable loss of function of nerves which should serve the muscles support the hypothesis that most cases of myasthenia gravis are associated with a primary motor nerve disorder. An autosensitization process in which the muscle is injured by specific antibodies has also been implicated in certain cases.

HISTOCHEMICAL RESEARCH

Two studies by the Institute did not confirm studies done elsewhere: so-called fetal myoglobin was not found in muscular dystrophy patients; and the fetal pattern of lactate dehydrogenase isoenzymes was found in additional diseases so that it could not be considered a specific test for muscular dystrophy.

The variations previously reported in periodic paralysis at present are not considered to be the hallmark of distinct types. In some cases of this disorder, "mitochondrial aggregates" (abnormal collections of tiny substances in only certain types of muscle fibers newly defined by the Institute) have been demonstrated by the techniques of histochemistry.

ANIMAL RESEARCH

The famous inbred strain of mice with symptoms closely resembling human MD continues to provide investigators with a valuable research device; other animals also aid the process of research. For example, dystrophic chickens permit research tests which offer parallels for human MD.

TREATMENTS BRING TEMPORARY RELIEF

Although no cure has been found for the various neuromuscular ailments, certain treatments are relieving symptoms temporarily. The new drug, valium, helps to control involuntary movements during muscle weakness or spasticity. Changes in the ionic balance help some patients with periodic paralysis. ACTH, well known in the treatment of arthritis, may relieve the pain of certain inflammatory diseases such as dermatomyositis.

FURTHER RESEARCH ON MYASTHENIA GRAVIS

Developments in the field of immunology, especially in regard to autoimmune diseases, have had an impact on neuromuscular research. Earlier predictions that myasthenia gravis might be an autoimmune disease have received preliminary substantiation. Grantees have determined that a constituent of serum from myasthenic patients varies in concentration in relation to the severity of the symptoms. The constituent, called serum complement, is involved in immune reactions of the blood. An abnormal globulin constituent from myasthenic patients binds to the serum complement as well as to muscle fibers. These results lend support to the hypothesis that the cause of myasthenia gravis may be based on an autoimmune reaction.

Also in relation to myasthenia gravis, a study has now been conducted to determine the effectiveness of ACTH. For more than 20 years adrenal cortical extracts have been used in treating myasthenia gravis patients. The usefulness, however, of ACTH in the treatment of the disease remained unsettled. This year, a study was conducted to test the effectiveness of ACTH on myasthenia gravis patients. Clinical investigators in six hospitals participated in the study. Forty-three patients were selected whose signs and symptoms were limited to the muscles around the eye. There was no evidence that ACTH produced improvement in the patients studied.

These investigators are now preparing for the evaluation of another suggested form of therapy in myasthenia gravis—removal of the thymus.

SPECIAL REPORTS: MULTIPLE SCLEROSIS

THE BACKGROUND

Multiple sclerosis is a common disorder of the nervous system characterized by recurrent episodes of paralysis, loss of sensation, and disturbances of coordination and vision. It is a disease of young adults—two-thirds of the cases being diagnosed between the ages of 20 and 40. Although the disorder is frequently disabling, recent data indicate that many individuals with this disease continue to live useful lives for many years.

Pathological examinations have established the fact that the fundamental disability consists of the liquefaction of the fatty substances within patchy areas of the central nervous system. In spite of the recognition of its general characteristics for almost 125 years, the cause and the mechanism of development are still unknown. During the past two decades, however, advances in scientific knowledge have made possible a coordinated attack to be focused on this disease. Now with increasing numbers of well-trained scientists available, a rapid intensification of the research effort is possible.

Allocation of Institute funds over the past 5 years for multiple sclerosis research has doubled—from $1,100,000 to $2,277,000. In addition to these funds, basic research programs concerned with the pathology, physiology, and chemistry of the brain are adding valuable information to the attack on multiple sclerosis.

THE RESEARCH PROGRAM

The Institute's multiple sclerosis program has been directed toward several promising leads:

Climate, an important factor

It has been well established that multiple sclerosis is a disease of temperate climates; it is almost unknown in the tropics. Multiple sclerosis is uncommon in the southern United States, but it is one of most common neurological disorders of the northern United States and Canada. Estimates indicate that, in the United States alone, as many as a quarter of a million individuals may be affected by this disease.

The Institute's program in epidemiology is attempting to determine the meaning of this unique distribution of the disease. Whatever the factor is that operates in the cold climate, its effect is a slow one. Several years of living in a high incidence region are required before the disease develops. Conversely, individuals moving from a cold climate to a warm one may develop the disease a number of years after leaving the high incidence area. Efforts are being made to determine the nature of the climatic or geographic factors significant in this odd relationship.

Biochemical studies of myelin

The outstanding feature of multiple sclerosis is liquefaction of the fatty sheath surrounding the nerves. To find the reason, a major focus of the Institute's program has been on the chemical processes involved in the formation and destruction of the sheath, called myelin. Approximately 57 percent of grant support in multiple sclerosis research is directed toward this end. The chemical structure of these fatty compounds has now been quite well established. Recent studies are demonstrating abnormalities of enzymatic constituents of these tissues in patients with the disease. Further observations also indicate that these abnormalities exist both in the areas of tissue destruction and in apparently unaffected regions of the brain of multiple sclerosis patients. It is still not clear whether these chemical abnormalities are a cause of the disease or a result.

Animal research

Another avenue of attack is devoted to the investigation of an experimentally produced disease of animals bearing a close resemblance to multiple sclerosis. This condition—experimental allergic encephalomyelitis (EAE)—characterized by a breakdown of the fatty nerve sheath, can be induced in healthy animals by inoculating them with brain tissue from other animals. The inoculated animal develops an immunity against the brain tissue, and in so doing, develops an immune reaction against its own brain which leads to self-destruction. While action of EAE bears close resemblance to multiple sclerosis, there still is great uncertainty as to whether this resemblance may be more superficial than real.

Using the experimentally produce condition as a model, efforts are being made to determine the nature of the chemical processes involved, and to develop a preventive treatment for the affected animals. The protein fractions of the brain which are responsible for inciting the disease have now been isolated and purified. In addition, electron microscopic examinations of the affected brain are being used to demonstrate the exact site of the destructive process.

Investigations of myelin are being facilitated by an Institute grantee's recent discovery for producing demyelinization in brain cell cultures. Under these circumstances one can observe the liquefaction of myelin when cells in tissue culture are exposed to the serum of an animal with EAE. Even more important, it has now been demonstrated that the serum from patients suffering with multiple sclerosis frequently contains an antibody capable of producing this phenomenon. Thus, today, there is strong evidence that the process of the animal disease, experimental allergic encephalomyelitis (EAE), has close resemblances to the human disease, multiple sclerosis.

Experimental control of demyelinization

At least three means have been developed for suppressing the animal disease EAE. Property spaced injections of the same antigen which produces the disease may have the effect of protecting the animal against it, just as the hay fever sufferer may be spared from his attacks by proper injection of hay fever antigen. New drugs developed to prevent the growth of cancer cells, and characterized by their ability to block nucleic acid formation, have been shown to prevent the development of antibodies in animals with allergic encephalomyelitis. During the period of their administration, the new drugs will prevent the occurrence of brain destruction. Cortisone, ACTH, and other drugs which interfere with immunity, have a similar but less striking protective effect. Some of the drugs with apparent value are now being tested with patients.

Virus studies

Although the autoimmune process may be the mechanism whereby the brain destruction takes place, it is still not clear what initiates the autoimmunity. One recent theory suggests that recurrent nonspecific virus diseases may precipitate the attack. On the other hand, it is possible that there is a specific virus responsible for this disease. The demonstration that viruses may lie dormant in the nervous system for long periods of time in other diseases, such as herpes and the disease of sheep called scrapie, lends support to this possibility. For this reason, the Institute over the last 2 years, in cooperation with the Fish and Wildlife Service, has attempted to transmit a virus into the brains of animals from patients with multiple sclerosis and other chronic inflammatory diseases of the nervous system. The completion of facilities at Patuxent during 1964 should facilitate this important work.

EVALUATION OF NEW TREATMENTS

From time to time reports occur of dramatic cures for multiple sclerosis. Hopes are temporarily raised, but none of these reports have been substantiated. Because of the recurrent and remittent nature of multiple sclerosis, the evaluation of the effectiveness of a cure is extremely difficult. The trial of a new treatment in three or four seriously ill patients may frequently be followed by recovery which is characteristic of the natural pattern of the disease, and is not attributable to the therapy. Many months of painstaking work are required to ascertain the true facts.

GUIDELINES FOR THERAPY

A the time of the Conference on Drug Therapy organized by the Institute in 1960, a panel was formed to establish guidelines for the evaluation of therapy in multiple sclerosis. The panel's studies have developed a protocol which outlines the problems to be considered, and the methodology required for meaningful results. Limited pretests have now been made with certain new drugs and also with some previously highly controversial therapy.

THE GOAL FOR FUTURE RESEARCH

Institute scientists believe that multiple sclerosis is beginning to yield to the broad new attack utilizing the multidisciplinary approach to its problem. The increase in funds has provided more highly trained manpower and refined facilities. These both are fundamental to intensifying research across a broad front and bringing each new finding into proper focus. With the increased facilities and manpower, the Institute's multiple sclerosis research program for fiscal year 1965 should rapidly advance and provide some of the greatly needed answers to demyelinating disorders.

SPECIAL REPORT: EPILEPSY

THE PROBLEM

Epilepsy, a group of conditions characterized by recurrent seizures, is believed to afflict at least 1 in 200 persons, or approximately 1 million Americans. Sporadic seizures are even more frequent. A number of studies have indicated that approximately 7 percent of the population have at least one convulsion during their lifetime. The majority of these are convulsions of infancy.

Epilepsy represents one of the most serious social problems within our society. Although the occurrence of an occasional seizure may represent a very limited disability, the social ostracism which results from this condition leads to far greater disability than the disease itself would indicate. It is one of the few remaining disorders where secrecy is often important to the sufferer. Therefore, complete control of seizures is an unusually important objective. With present therapy, complete control is possible in an estimated 50 percent of cases and marked reduction of seizures can be accomplished in a large percentage of the remainder. However, possibly 20 percent are still highly resistant to currently available therapy.

CLASSIFICATION OF SEIZURES

Epilepsy should not be looked upon as a disease. It is a symptom which results from many different causes. In a large percentage of cases, seizures are the result of a brain injury from asphyxia, infection, physical impact, or chemical abnormalities or some anatomical defect of the brain such as tumors or congenital malformations. Thus, almost any brain disease or injury can be associated with convulsions. In some instances, seizures may result from chemical or metabolic disturbances. In some cases, susceptibility to seizures may contribute to their occurrence. In other cases, a genetic trait appears to be the essential factor.

In view of the multiplicity of causes of seizures, the classification of the epilepsies has proven a most difficult task. Historically, the epilepsies have been classified on the basis of the predominant clinical characteristics of the seizure. "Petit mal" refers to minor episodes characterized by transitory lapse of consciousness without gross motor movement. "Grand mal" refers to generalized convulsive seizures preceded by sudden loss of consciousness. "Psychomotor" refers to seizures characterized by automatic or involuntary behavior associated with impairment of recollection or consciousness, and "focal" refers to seizures whose characteristics indicate that they have originated from some demonstrably localized area of the brain.

More recently, seizure classifications have been developed which refer specifically to the area of the brain in which the seizure appears to originate, or is largely expressed. The further refinement of seizure classification has been made possible by the development of the electroencephalograph. This instrument records the electrical activity of the brain, showing the varying patterns with greater or lesser relationship to the focus of the discharge and aids in diagnosing the disorder.

Attempts to classify seizures on the basis of the chemical susceptibility of the patient can serve as an interesting research approach, but to date have not shown sufficient consistency to be very useful.

HISTORY OF SEIZURES

Because of the increasing evidence that the nature of the epileptic process varies with the age of the indivdual, and in the expectation that this will throw new light on seizure mechanisms, the Institute this year sponsored an international conference to review these aspects.

A clearer understanding of the epilepsies is being derived from correlations of anatomical development of the brain with the seizure patterns observed in different age groups of man and animals. The immature brain has a heightened susceptibility to seizures as evidenced, for example, by the frequency of their occurrence in association with febrile illnesses of childhood. Seizures occurring in the infant prior to 6 months ordinarily are a manifestation of severe brain damage or disease. Such seizures are likely to be focal and take the form of alternating rigidity and relaxation of muscles, called myoclonus, but with poorly organized patterns. The myoclonic form of epilepsy, however, is particularly common between the ages of 6 months and 4 years. The accompanying EEG patterns are slow diffuse waves called hypsarrahythmia. Mental deterioration is common.

It is not known at this time whether the myoclonic seizure leads to brain injury, or is the result of serious brain diseases occurring in childhood. In some instances, myoclonic epilepsy is, in fact, merely a symptom of virus encephalitis. In other instances, the occurrence of rather dramatic improvement through the use of ACTH or cortisone suggests that inflammatory or chemical changes are important in its development. The Institute has established a virus isolation program, in which a search for an infectious agent will be made by injecting into animals biopsy material from infants seriously afflicted by this disease.

From the age of 4 years to puberty, petit mal seizures are far more common than they are at other ages. This type of seizure, sometimes called centrencephalis because it appears to involve centrally located brain structures, represents a unique problem for a number of reasons: its particularly limited age range, its association with a strong hereditary factor, its characteristic low seizure threshold, and its unique response to medication.

As the child grows older, the petit mal attack no longer remains confined to the deep structures. Generalized convulsions now make their appearance. The minor episode is likely to be replaced by generalized seizures. Not infrequently with the passage of puberty, all forms of seizures may disappear. For this type of disability, it is the hope of medical therapy that the seizure can be controlled until natural developmental changes in nerve organization and sensitivity may raise the seizure threshold. Additional research is needed on the underlying structure and chemistry of the nervous system unique to this age period which may be responsible for these changes.

In animal experimentation, correlations are being made between the seizure susceptibility of the brain and the development of the cortical brain cells and of their synaptic relations.

MECHANISMS OF SEIZURES

The essential feature of the epileptic attack is the occurrence of sudden, intense, repetitive and synchronous discharges of groups of nerve cells, or neurons. The clinical expressions of the attack, such as impaired consciousness, loss of willed activity, and convulsive phenomena, are reflections of the overactivity of the nerve cells. A primary objective of the Institute's research on epilepsy is to understand the intricate mechanism responsible for the nerve discharge.

Full understanding of this process requires precise knowledge of the structure, chemistry, and function of the cellular components of the nervous system, their interrelationships in health and disease, and various methods by which these processes can be altered or controlled.

The development of sensitive amplifiers and of the EEG has ushered in a new era in the study of the nervous system. These instruments have made it possible to study the electrical discharge from the brain cell, including electrical changes inside and outside individual cells. Such amplifiers are also being applied to the study of synchronous electrical changes within a given mass of cerebral tissue. Whereas the electroencephalograph permits the study of synchroms activity within the large masses of cells of the brain, the microelectrode permits the study of the activity of relatively small numbers of units within the complex brain structure.

These methods have led to tremendous advances in knowledge of the brain cell activity underlying normal and abnormal brain function. Such methods, nevertheless, currently provide only limited knowledge of the complex interactions which occur among the billions of cellular units. Only a beginning has been made in exploiting the new techniques of computer analysis which are applicable to this problem. In this connection, the Institute has supported several independent studies, and has contributed to the support of a newly developed computer center for neurological research at the University of California at Los Angeles.

The electroencephalogram, or EEG, reveals striking electrical phenomena in association with the seizure. Psychomotor epilepsy is most commonly focal in origin, with the focus located in the temporal lobe. In grand mal and petit mal, the EEG record between seizures may be relatively normal. The episode itself is sudden in onset and is characterized by its diffuse manifestations. The occurrence of synchronized changes in both cerebral hemispheres suggests that there is probably a central pacemaker for the electrical discharge of brain cells. It also suggests that the primary focus for this type of disorder may lie in deep-seated regions of the brain which are centrally located. The term "centrencephalic" has been coined to refer to this possible focal point.

Little recognition has been given to the fact that focal forms of epilepsy are frequently associated with clear-cut brain damage, whereas the centrencephalic forms are less commonly associated with such evidences but are more often associated with genetic susceptibility in the family history. There may be essential differences in the fundamental mechanisms of these several forms of epilepsy. The discovery of several methods for producing focal epilepsy in animals has made possible the extensive investigation of this phenomenon.

Chronic epileptic conditions in animals can be created in several ways: freezing of the cortex, injection of aluminum hydroxide cream into areas of the brain, and the use of other metallic irritants. For acute conditions, the local application of penicillin produces a focal discharge which appears to be identical with the chronic condition.

Of particular research interest is the occurrence of a secondary focus subsequent to the production of a primary focus produced in animals by one of these techniques. The study of electrical and chemical changes in the primary and secondary foci is thus of profound interest. Equally challenging is the production of an epileptic focus through the isolation of a portion of cortex by undercutting. When undercutting is incomplete, it may serve as a trigger for recurrent seizures. The overactivity of this isolated cortex may be the result of chemical changes secondary to this interruption of different nerve pathways. Another theory postulates that it is the result of misdirection of regenerated severed nerve endings or axones, with the creation of self-activating looped circuits.

In any event, microelectrode studies have demonstrated that brain cells within the affected area exhibit highly abnormal behavior. Recorded electrical activity between seizures is cheracterized by deviations of the resting potential of the cell and unusual fluctuations of this potential. Seizure activity shows even wider fluctuations of electrical potential with the occurrence of dramatic high-frequency discharges during the height of the seizure. The meaning of these deviations of electrical potential in terms of synaptic, dendritic, neuronal, and axonal behavior is under intensive investigation.

THE CHEMICAL ASPECTS OF SEIZURES

Seizures may be caused by a wide variety of metabolic conditions and chemical agents. They accompany such metabolic derangements as hypoglycemia and phenylketonuria. The threshold for seizure induction may be elevated by bromides or anticonvulsant drugs. Full information regarding the basic chemistry and pharmacodynamics of nervous activity, therefore, could contribute much to our knowledge of epilepsy and our potential for its control.

The discovery in 1954 that vitamin B_6 (pyridoxine) deficiency was associated with a convulsive state, as well as the demonstration of similar conditions produced by antimetabolites of the vitamins, strongly implicated derangements of certain metabolic pathways as underlying mechanisms for seizures. This possibility had already been suggested by the observation of deviations of the amounts of acetylcholine and cholinesterase in anatomical areas of focal epilepsy. Investigations of the relevant metabolic pathways converged on those involving the glutamic acid-glutamine and aspartic acid-asparagine group of amino acids, which require pyridoxine for many aspects of their metabolism. Since abnormalities in the metabolism of these amino acids were found in a number of seizure states, the Institute undertook an extensive investigation of the effect of one member of the group, asparagine, in clinical cases of epilepsy, mostly of the petit mal type. Studies indicated that although this agent, which was quite costly, had limited practical applicability, it was effective in modifying seizure activity in a significant number of patients.

These observations stimulated continued exploration of the amino acid constitutents of the central nervous system. More recently, these agents have been demonstrated to be important as precursors of gamma-aminobutyric acid, an agent having important inhibitory effects on nerve activity. It is now clear that convulsions due to a deficiency in pyridoxine are related to a decreased production of gamma-aminobutyric acid from its immediate precursor, glutamic acid. Deficiencies of the vitamins are an occasional cause of seizures in infancy and childhood, and pilot investigations at the Institute indicate that gamma-aminobutyric acid, in some cases, can be an effective anticonvulsant in these and other types of clinical seizures.

There is need for further intensive investigation of the role of acetycholine gamma-aminobutyric and related amino acids, and other agents in influencing nerve excitability, especially as it relates to the distributions and movements of electrolytes across nerve membranes. It is possible that it is modifications in the amount, or metabolism of these agents, which lead to lowered seizure thresholds in affected areas of brain tissues.

MEDICAL TREATMENT

The mainstay of the Institute's therapeutic program for epilepsy is the elevation of seizure threshold by the use of anticonvulsant drugs. The discovery of diphenylhydantoin (Dilantin) in 1937 represented a most important advance. Not only has this drug continued to be one of the most valuable single agents in the control of seizures, but in addition its discovery illustrated the value of developing experimental methods for the testing of anticonvulsant action in animals. The methodology for such screening has been further elaborated since that date, and drugs may now be tested in animals for clincal effectiveness against grand mal, petit mal, and psychomotor seizures. The rapid recognition of the clinical efficacy of trimethodione (Tridione) for petit mal within 2 years after its synthesis as a potential analgesic is attributable in large measure to availability of the appropriate anticonvulsant screening procedures in animals.

The development of new drugs has rested largely with commercial producers. New drugs tested have been mostly modifications of barbiturates, hydantoin, and Tridione, and a rather extensive armanentarium of drugs has been developed. In addition, drugs developed as analgesics or tranquilizers also are commonly tested for anticonvulsant properties. The crucial need, however, is for more accurate information regarding the relationship between chemical structure and pharmacological action.

The Institute's program has concentrated on studies relating to the basic mechanisms of action of anticonvulsant drugs. In spite of structural similarities, there are important differences between phenobarbital and Dilantin. Whereas phenobarbital acts to elevate the threshold of nerve excitability generally, Dilantin has little effect on normal thresholds but appears to stabilize affected membranes and prevent spread of seizure activity. There is an opportunity at this time for reinvestigation of the role of anticonvulsant drugs in the light of newer knowledge of the electrical and chemical aspects of seizures.

Recently, it has been demonstrated by an Institute scientist that local cooling of the brain produces alteration in blood vessel permeability and allows the passage of therapeutic agents into certain portions of the brain. The possible utilization of this technique for the control of focal seizures is under investigation.

The determination of the best anticonvulsant or combination of anticonvulsants for a given patient remains a complex problem. The combination of phenobarbital and Dilantin is effective in a large proportion of the less-severe forms of convulsive disorder. In petit mal, the use of Tridione or related compounds often is necessary. When these more commonly used drugs fail, the physician must resort to any one of 10 or 20 additional agents which occasionally are effective. In the majority of instances these agents are not used singly, but in combination.

Only large-scale and scientifically conducted trials, with careful classification of seizures and clinical evaluation of drug effects, will provide the necessary knowledge for the proper utilization of these powerful agents. The development of such trials demands the talents of the practicing clinicians, yet few have had interest or experience in the specialized techniques required for conducting such therapeutic evaluations.

In May 1960, the Institute organized a symposium on the methodology of drug evaluation. One of the panels at this symposium addressed itself to problems of the evaluation of anticonvulsant agents. The panel indicated that the development of such trials required a workable classification of cases, an ethical method for modification and matching of therapeutic agents, and a reliable and consistent method for evaluation of effectiveness. None of these requirements could be fulfilled at that time.

Since the meeting, members of the panel have continued to work toward the development and pretesting of these required methodologies. This group is now undertaking a limited pretest trial, comparing the effectiveness of two of the more commonly used anticonvulsant agents as a step in the development of methodologies for broader scale testing.

SURGICAL TREATMENT

Since its inception, the Institute has continued a program for the elaboration and evaluation of surgical therapy. In well over 50 percent of selected cases, the results are highly satisfactory. For a number of years, it has been recognized that surgical excision of the irritative focus in focal epilepsy may permanently abolish seizures. The method has particular appeal because it represents cure rather than control. Its usefulness, however, is restricted to those individuals with a clearly defined focus, and in whom the focus is so located that removal of the surrounding healthy brain tissue will not produce a neurological deficit. Also, in surgery, the creation of a secondary scar must be avoided since it can cause recurrence of seizures. Surgical treatment has been applied particularly to temporal lobe (psychomotor) seizures, since large portions of this area of the brain can be removed with only moderate impairment, and since the medical control of such seizures is often poor.

TRAINING AND RESEARCH FOR EPILEPSY

For the development of its broad program, the Institute has relied heavily on training programs in neurophysiology, neurochemistry, and clinical neurology. An adequate supply of highly trained scientists for the conduct of fundamental investigations has been the essential need. At the present time, the Institute is supporting 14 training programs in neurophysiology and neurochemistry amounting to $661,582 per year.

Research grants relating to epilepsy and amounting to $2,024,347 have currently been awarded. At the Institute's Bethesda laboratories, there are 11 research projects relating to epilepsy, amounting to $388,079. It must be emphasized, however. that these figures do not include a number of research grants in the general field of neurophysiology and neurochemistry which bear varying degrees of direct relevancy to this problem area. There are 359 such "unspecified" research awards amounting to $8,824,406 to date in fiscal year 1964.

DISSEMINATION OF KNOWLEDGE

During the evolution of its program, the Institute has continued to maintain an overview of the field, and especially has concerned itself with the rapid dissemination of knowledge regarding research developments. Thus, the Institute has sponsored or supported the following symposia:

Symposium on Subcortical Implanted Electrodes, Georgetown University School of Medicine, Washington, D.C.
Workshop on Epilepsy, New York, N.Y.
Symposium on Abnormal Nervous Function, Boston, Mass.
The EEG in Infancy, Baylor University, College of Medicine, Houston, Tex.

In many instances, a continuing review of this field also is maintained by the several scientific societies with direct interest in this disorder. Thus, the American EEG Society has organized the following symposia and the proceedings have been published in the EEG Journal—Electroencephalography and Clinical Neurophysiology, where much of the basic research regarding the electrical phenomena of the epileptic discharge is also published:

1963: What the Brain Waves Tell the Brain. Problems in EEG Interpretation.

1962: Symposium on 14–6/second Positive Spiking. The EEG in Relation to Space Travel.

1961: Medicolegal Symposium. Symposium on the Physiological Basis of Memory.

1960: Symposium on Basic Mechanisms in the Epileptic Discharge.

1959: Colloquium on Teaching Methods in Electroencephalography. Symposium on Conditioning of EEG in Animals and Man. Joint Symposium with Society of Biological Psychiatry on the Significance of Gamma-amino Butyric Acid (GABA) in the Brain.

Similarly, the American Epilepsy Society at its annual meeting, in addition to general papers of current interest, has presented the following symposia:

1963: Symposium on Behavioral and Mental Changes Associated with Seizures.

1962: Symposium on Petit Mal Epilepsy.

1961: Phylogenesis and Ontogenesis of the Epileptic Seizure: A Comparative Study: Synaptic Organization of the Immature Cortex; Maturation of Cortical Substrata of Epileptic Events.

1960: Changing Concepts of Focal Epilepsy.

1959: Symposium on The Basic Mechanisms of Anticonvulsant Drugs.

Some of these have been published in the journal, Epilepsia:

Symposium on Basic Mechanisms of the Epileptic Discharge. Cape Cod, Mass., June 11, 1960.

Symposium on Post-Traumatic Epilepsy. New York City, December 11, 1958.

Symposium on ACTH, Adreno-cortical Hormones and Juvenile Epilepsy. Paris, France, December 1, 1960.

Symposium on Reflex Mechanisms in the Genesis of Epilepsy. Prague and Liblice, Czechoslovakia, September 26–29, 1960.

EVALUATION OF NEW DRUGS

Mr. Fogarty. Did you develop anything new in the last year for epilepsy?

Dr. Masland. Each year, there are additional new drugs and there are two new ones this year which are helpful in selected cases. Our main concern now is the development of a strong program for the rapid evaluation of new drugs. New drugs are being produced rather rapidly by a number of drug companies, but they are anxious to have us develop a mechanism whereby they can be rapidly evaluated. This we are getting ready to do.

STROKES

Mr. Fogarty. What about strokes?

Let's see. The President in his health message—did he set up a Presidential Commission on strokes and cancer?

Dr. Masland. Strokes, heart disease, and cancer.

Mr. Fogarty. Did he set one up or recommend the setting up of one?

Dr. Masland. It was just a recommendation. I do not know whether it was actually done.

Mr. Fogarty. I think President Kennedy was about to make a recommendation. Were you people asked to report on this?

Dr. Masland. I am not aware of any request. So far, we have no word about how the new effort that President Johnson mentioned is going to be organized. We have made some progress in strokes. Not as much as we would like but definite advances. We have a special report on strokes.

(The report referred to follows:)

Special Report: Cerebrovascular Disease

Cerebrovascular disease is the third ranking cause of death in the United States and is a major cause of chronic disability. It includes those disorders of one or more of the blood vessels supplying the brain, leading to damage of the central nervous system.

Stroke is the most common type of cerebrovascular disease, and is usually due to one of three reasons: (1) Thrombosis—the presence of a blood clot which remains at its point of formation and prevents the flow of blood; (2) embolism—the sudden blocking of a blood vessel occurring when a blood clot or other abnormal particle, carried by the blood from a larger to a smaller vessel, plugs the smaller vessel, and (3) hemorrhage—the rupturing of a blood vessel so that blood leaks into surrounding tissue.

The National Institute of Neurological Diseases and Blindness is concerned with the problem of cerebrovascular disease and particularly with the neurological disturbances that result. The Institute has a comprehensive research program in cerebrovascular disease, including numerous research projects, several cooperative and collaborative studies, and three cerebrovascular research centers.

CEREBROVASCULAR RESEARCH CENTERS

Investigators at the three research centers, located in Minneapolis, Detroit, and New York City, are involved in studying the many facets of this problem, including improved methods of diagnosis, treatment, and prevention as well as the etiology and pathogenesis (cause and development) of this disease.

The scientific team of the Cerebrovascular Research Center at the University of Minnesota is investigating the neurological aspects of cerebrovascular disease, including basic mechanisms of circulation and nutrition of the brain. Clinical studies are being extended to include investigations of some of the more basic mechanisms in the pathology, physiology, and chemistry of the brain.

At the Wayne State University Cerebrovascular Research Center, investigators are particularly concerned with anticoagulant and fibrinolysin therapy, cerebral blood flow, lipid metabolism in cerebrovascular disease (including the effects of cholesterol inhibition and calcium binding substances) and arteriographic and cinematographic studies of cerebrovascular disease.

The program at the Cornell University Medical College embraces such areas as the natural history of cerebrovascular disease, improved methods of diagnosis, treatment with particular emphasis on anticoagulant and surgical therapy, the clotting mechanism, the role of the thrombolytic (clot dissolving) mechanism and thrombolytic agents, and the role of lipids in the pathogenesis of cerebrovascular disease.

COOPERATIVE STUDIES

Through the years, the Institute has organized and supported a number of cooperative studies on cerebrovascular disease. These studies have enabled leading scientists in widely separated locations to concentrate on specific aspects of cerebrovascular disease.

A significant contribution to cooperative research in this field was the publication of the report of the Institute ad hoc Committee on Cerebrovascular Disease, "A Classification and Outline of Cerebrovascular Disease." This report helped to establish reliable criteria for diagnosis and research in this field. It also provided the base for a cooperative study on the use of anticoagulants in the therapy of strokes. The results of this study, now being published, will provide the medical community with the most up-to-date information regarding the usefulness of anticoagulants in each type of stroke as defined in the original classification. As a result of the experiences in this cooperative study, some refinements are being made to the classification.

The Institute has recognized the incompleteness of criteria for making appropriate medical decisions about treatment of intracranial hemorrhages. In 1956, it appointed a committee of leaders in cerebrovascular research to review the status of the field and recommend an approach for obtaining this clinical information. The committee realized that no individual or clinic in this country could accumulate enough cases to answer many of the questions which have persistently confronted physicians and surgeons treating patients with this condition. As a result of the committee's recommendations, the Institute established a cooperative study of intracranial aneurysms and acute subarachnoid hemorrhage in 1957 with a central registry at the State University of Iowa.

The first phase of the study was conducted from 1957 to 1962. During this period the necessary research protocol was developed, and the four most promising treatments for cerebrovascular aneurysms were identified. Investigators demonstrated that under certain conditions patients could be helped by each of these four methods.

The second phase of the study, begun in 1962, is concerned with differentiating when, or under what conditions, each of these four therapies is most applicable. Twenty-one cooperating laboratories (including one in Great Britain) are submitting their data to the central registry, where it is being pooled and analyzed. The study gives promise of providing improved criteria to the medical community concerning the treatment of this medical emergency.

EPIDEMIOLOGICAL STUDIES

The Institute is supporting a cooperative epidemiological study on cerebrovascular disease under the auspices of the World Federation of Neurology (WFN). The objective of this study is to establish correlations among degenerative changes in the cerebral vessels found at autopsy, environmental conditions, and other factors such as sex, age, race, culture, diet, and geographic influences.

Scientists from several nations, including Italy, Poland, Norway, Peru, Mexico, England, and the United States, are either participating in this WFN study or are conducting independent parallel studies.

Three separate but parallel collaborative studies on the pathology of cerebrovascular disease have developed in conjunction with the main epidemiological investigation. These parallel studies were initiated in response to the need for more detailed information about the basic pathology of cerebrovascular disease. They include studies of the large vessels at the base of the brain, research on the severity of arteriosclerotic changes in cerebrovascular disease, and investigations of the structure of the wall of the blood vessel.

JOINT SUBCOMMITTEE

Cerebrovascular disease is a problem of common concern to the National Heart Institute and the Neurology Institute. In recognition of this mutual responsibility, and in order to provide for a coordinated aggressive attack on cerebrovascular disease, a Joint Council Subcommittee on Cerebrovascular Disease was formed in 1961. Composed of Advisory Council members from both Institutes and other consultants having particular interest and experience in cerebrovascular research, the Subcommittee is charged with the continuous review of research progress in the area, identifying research and training needs, and recommending needed new program developments. Examples of the activities of the Joint Council Subcommittee follow.

A panel of the joint subcommittee organized the Fourth Princeton Conference on Cerebrovascular Disease held in January 1964. Sponsored by the American Neurological Association and the American Heart Association and supported by a Neurology Institute grant, the conference was concerned with the most promising advances in the field since 1961. Participants at the conference were selected because of their important contributions to specific aspects of the cerebrovascular area.

The conferees considered various methods of improved diagnosis, including angiography, new techniques for measuring regional cerebral blood flow, the latest application of radioactive gases to diagnostic procedures, and rheoencephalography. In angiography, a substance that is opaque to X-rays is injected into the blood vessels feeding the brain and then an X-ray picture is taken, thus making it possible to visualize the vascular system of the brain.

Although angiography is considered one of the best available diagnostic aids, it does have its shortcomings, and research is in progress to improve the effectiveness and safety of the technique. The principal problem in cerebrovascular diagnosis has been the inability to view the total circulation of the brain directly through the skull. A new method, called the subtraction technique, has been developed to overcome this difficulty. It consists of a photographic process utilizing electronic recording devices which can cancel out all X-ray images (including those of the skull) except the opaque material outlining the vascular system of the brain.

Therapeutic agents evaluated at the Princeton conference included anticoagulants, thrombolytic agents, and hormones (estrogen). Another therapeutic measure, hyperbaric oxygen therapy, also was discussed. This procedure involves subjecting a patient to oxygen at higher-than-normal pressure, thus saturating the blood and tissue with a greater amount of oxygen than would be possible at normal pressure. The extra oxygen added to the blood might, in some cases, forestall permanent damage to brain tissue and give time to correct the defect.

The conferees also learned more about the National Heart Institute's collaborative study on surgery of occulsive disease of blood vessels in the neck. In this study patients with symptoms of cerebral arterial insufficiency are being studied by angiography and other diagnostic techniques to determine the importance of blocked blood flow in neck arteries supplying the brain. Those with occluded arteries, who are judged likely to benefit from surgery, are operated upon to remove or bypass the obstruction to blood flow. It is hoped that the study may result in improved criteria for selecting patients for surgery and for determining the optimum form of treatment.

Transactions of the fourth conference will be distributed by the subcommittee as were the transactions of the third Princeton conference in 1961.

The Joint Council Subcommittee also was responsible for the wide distribution of the Neurology Institute's cerebrovascular study group report on cerebrovascular disease in 1962. A critical analysis of the status of cerebrovascular research, the report has been used as a technical resource in medical schools and as a reference in research. It complements the proceedings of the Princeton conferences as a means of scientific communication to the medical and scientific community. The report is being revised for publication in 1965. It will again be distributed widely as a research and teaching aid.

The "Cerebrovascular Bibliography," prepared with the cooperation and assistance of the National Library of Medicine, is providing a continuing index of research on cerebrovascular diseases. It is being evaluated as a permanent tool for researchers in cerebrovascular disease. Currently, scientists are analyzing the usefulness of this technique as an index to the National Library of Medicine's new medlars system (medical literature analysis and retrieval system).

The Joint Council Subcommittee is organizing a national workshsop on the epidemiology of cerebrovascular disease to be held in June 1964. At this workshop, national leaders in epidemiology, neurology, and cardiology will evaluate the present status of knowledge on the epidemiology of stroke, will crystallize the needs, and recommend appropriate steps for obtaining this information.

PROSPECTS FOR THE FUTURE

Since its founding in 1950, the Institute has supported research which has resulted in important advances in diagnosing and treating patients with cerebrovascular disease. However, in spite of the progress that has been made, the morbidity and mortality figures for patients with cerebrovascular disease continue to increase.

There is still no accurate method of predicting who may develop a stroke, and practically no way of knowing who has had a stroke unless there are clinical signs. One of the goals in the diagnosis and treatment of stroke patients is to develop techniques which might be used before permanent damage to the brain occurs. Early detection by angiography has been most helpful in speeding accurate diagnosis. This technique needs to be refined; its safety and convenience should be increased.

Additional knowledge of the blood clotting process and the action of therapeutic agents, such as anticoagulants, fibrinolysins, and hormones, should lead to increased success in treatment.

The surgical successes to date have been concerned primarily with the repair of the extracranial arteries. New procedures must be developed for treating patients with intracranial disorders.

The Institute is supporting nearly 100 investigations on the various clinical and basic science aspects of the overall problem. However, there continues to be a critical shortage of qualified neurologists and related scientists to serve as scientist-physicians and teacher-investigators. As new techniques are developed, even more of these specialists will be needed.

In recognition of this need, the Institute has been providing the major support for superior research training environments and for personal support of selected individuals who have been receiving training. Currently, the Institute is supporting research training programs at institutions where approximately 600 graduate physicians and scientists are being prepared for specialization in neurology, neurosurgery, and the related neurological sciences, such as neuropathology, neuroanatomy, and neurophysiology. These specialists of the future are learning to employ the latest scientific techniques and procedures. In a few short years, they will be making contributions toward preventing, alleviating, and curing disease by developing still newer, more improved diagnostic

and therapeutic procedures, and by adding to the fund of knowledge concerning the causes of neurological diseases, including cerebrovascular disorders.

Dr. Masland. We are working very closely with the Heart Institute in the development of a program. We have a joint subcommittee of the two councils to advise us, and to work on this area. This group is holding regular meetings. They have published reports on areas of research opportunity. Working with the National Library of Medicine, they are publishing a bibliography on vascular disease, so anyone working in the field will have that information available at his fingertips. The joint subcommittee organized a series of international conferences. The most recent was held in January.

We have developed three large centers for the study of strokes. One is in New York, one in Minnesota, and one in Detroit, at the Harper Hospital.

Mr. Fogarty. Where is the one in New York?

Dr. Masland. That is Dr. Wright's program at Cornell.

Mr. Fogarty. And the one inDetroit?

Dr. Masland. At the Harper Hospital. This is at Wayne State University.

Mr. Fogarty. Where is the one in Minnesota?

Dr. Masland. That is Dr. Baker's program at the University of Minnesota.

Mr. Fogarty. Oh, yes.

Dr. Masland. Each of these three programs has a different emphasis. Dr. Wright is primarily working on blood clotting, coagulation, and the study of anticoagulants. I have a report from him.

Dr. Baker is working largely on epidemiology. He has a cooperative project with Dr. Katsuki in Japan. They are working together to obtain accurate information on the nature of arteriosclerosis in the cerebral vessels in persons in Japan as compared with persons in Minnesota.

The one at Detroit is primarly evaluating therapy for strokes.

They have studied over 500 patients with strokes using the method of visualizing of blood vessels called arteriorography. They have done a thorough study, and have well documented the safety of this procedure and its value.

They have also been working with anticoagulants, and I think we can say now, definitely, that anticoagulants do have a place in the treatment of strokes.

Mr. Fogarty. After the stroke has occurred?

Dr. Masland. Particularly while it is in progress.

Mr. Fogarty. While it is in progress?

Dr. Masland. If you catch a person early in the development of the stroke before it has fully matured, you can modify the process.

STROKE SYMPTOMS

Mr. Fogarty. How does it happen? What are the first symptoms or the first effects of it?

Dr. Masland. It depends. There are three kinds of strokes. One is due to hemorrhage; one is due to the plugging of the vessel by a clot, coming, for example, from the heart; and the third is by clotting.

The symptoms are a little bit different.

In the case of hemorrhage it usually strikes suddenly. Usually you have a tremendously severe headache. And just like that it hits you.

Embolus is also quite sudden. A person can be working along and hit the floor.

Thrombosis is more likely to be gradual. A person gets up in the morning a little weak on one side of the face. His hand is a little weak and he goes to bed. Later on in the day, his whole arm is paralyzed and maybe the next day his leg is paralyzed.

Mr. FOGARTY. It does not happen in a second?

Dr. MASLAND. No; if he can get to the doctor right at the beginning, the anticoagulant can be valuable in preventing further extension of the paralysis.

Mr. FOGARTY. The other two do not give you time?

Dr. MASLAND. No: of course, you would not want to give an anticoagulant to a person with a hemorrhage.

Another related condition is the "transient ischaemic attack." Individuals have minor dizzy spells or momentary periods of loss of speech for 15 or 20 minutes. This is a warning that a stroke is impending and in these cases, the use of an anticoagulant is extremely valuable.

One of the problems here is that that form of treatment requires a highly trained specialist to give it. You have to select the patient. You do not want to give an anticoagulant to a person having a hemorrhage. Furthermore, the dosage has to be regulated very, very carefully.

Now here again, we are working with the Heart Institute to train some people and establish centers from which people trained in the use of this methodology can be sent across the country.

Neurologists are being trained in the use of blood coagulants. Men trained in internal medicine are learning about neurological diagnosis.

Mr. FOGARTY. Well, this is another area where the medical schools have not kept pace in the number of hours the medical student takes.

Dr. MASLAND. That is right.

HOSPITAL CARE FOR NEUROLOGICAL PATIENTS

The other thing I mentioned earlier is these chronic forms—not really strokes, but they are arteriosclerosis of the cerebral blood vessels. These people are in the State hospitals. They are even less remembered. There is less being done for them.

Mr. FOGARTY. What can be done for them?

Dr. MASLAND. This is what we discussed earlier. We should have a program to draw these into the orbit of medical research.

Mr. FOGARTY. You said something about making room for them in a general hospital?

A few years ago, I think it was suggested that general hospitals ought to make provisions for mental patients.

I was just wondering whether or not that is a parallel problem.

Dr. MASLAND. It is exactly the same problem. There should be, within the general hospital, some provision for these chronic cases and more particularly, in the teaching hospital.

Mr. FOGARTY. How can they afford to go to a general hospital?

Dr. Masland. They cannot. Again, this is one of the problems of neurological disease. The person with this kind of disease is disabled for long periods of time. He does not have the resources to provide for chronic illness.

Mr. Fogarty. If he cannot afford to go to a general hospital, maybe we had better start to do something in the State hospitals in bringing the general hospital to the State hospital in some way.

Dr. Masland. I think we ought to do both.

I think also that there is a most important problem in the teaching hospital. The teaching hospitals until recently have concentrated on acute illness and today this is not the most important and difficult problem in medicine. The important and difficult problems in medicine are chronic disease, so we have to find some means to bring chronic illnesses into the teaching hospital.

REGENERATION OF NERVE TISSUE

Mr. Fogarty. What about your work in the regeneration of nerve tissue that you spoke about last year?

Dr. Masland. In terms of regeneration in the peripheral nerves, there have been some very important advances in surgical techniques which have been developed in a center which we are supporting in New York. It has been demonstrated that a fairly long segment of nerve can be replaced.

Now, this is most important in traumatic injuries where a large segment of the nerve has been torn away. This can now be replaced, and the nerve will grow back in.

Within the central nervous system, the spinal cord and the brain, we have still not accomplished effective regeneration in the higher animals. Regeneration does take place in the lower forms—frogs and animals of this sort. So we are studying those animals to find out what their secret is; to see whether we can develop the means to accomplish this in higher animals.

We are also studying this in the embryo because we know that the same processses which lead to the formation of tissues in the embryo conceivably might be used to lead to the formation of new growths in the adult.

So our major focus now, for regeneration, is in embryology and in the study of this process in lower animals.

PUERTO RICO PROJECT

Mr. Fogarty. Now tell us about your project in Puerto Rico. How it is doing.

Dr. Masland. I have a special report on this area. You will recall that this project in Puerto Rico was established under the planning of Dr. Bailey when he was Director of the Institute and working closely with Dr. William Windle and it was developed as a part of the collaborative project. The concept was that problems of the perinatal period would be studied in the human within the "perinatal project" but that there were serious limitations on any human experiments. The collaborative project was merely to observe what happened; not to experiment. Experiments should be done in lower animals, and for this it would be necessary to have primates. There are two advantages of the primate. Its brain is more advanced, and its reproductive processes are more like a human's than those of many other animals.

Under Dr. Windle's guidance, this program has developed in a very strong fashion. We now have about 900 monkeys in Puerto Rico. Some of them are in the original island (we have two additional islands); and about 300 of them are breeding animals in the laboratory on the quarantine station.

Within this laboratory, it has been demonstrated that you can produce cerebral palsy in monkeys. You can produce it by asphyxiation, and by poisoning them with jaundice. Within some preliminary experiments, it has been possible to modify this process by changing the acidity of the blood and the glucose content of the blood in the asphyxiated animal.

This past year, Dr. Windle has resigned from that laboratory and is going to start a new research program with Dr. Rusk in New York. We now are recruiting a new chief of the laboratory. We have several excellent candidates in mind. Our proposal is to continue to develop this laboratory, to study the development of the nervous system and the modifications of the development which are occasioned by injuries in the perinatal period.

STATUS OF NEW FACILITIES

Mr. Fogarty. You are still at the quarantine station. What happened to your new building? I thought you would have that built by now.

Dr. Masland. Mr. Wipf, do you want to report on the building?

Mr. Wipf. We have prepared the program of requirements for the building—its technical features. We have finally completed the deed to the land from the Commonwealth of Puerto Rico, the medical center ground.

Mr. Fogarty. I thought they agreed to that a couple of years ago.

Mr. Wipf. They did but we are just now getting the final deed—the draft is ready. We have the program of requirements with NIH.

Mr. Fogarty. This is taking quite a long time.

Mr. Wipf. Apparently, the planning of a building seemingly takes longer than its construction.

Mr. Fogarty. You have an awful lot of trouble planning these buildings in the Public Health Service. Everything seems to be running a year or two behind. Are they donating the land?

Mr. Wipf. Yes.

Mr. Fogarty. Is that the same area where they thought it would be a couple of years ago?

Mr. Wipf. Yes; it is on the grounds of the medical center close to the university. I think plans also indicate that the medical school eventually will move out there, too.

Mr. Fogarty. That is going to be quite a medical center.

Dr. Masland. Yes.

Mr. Fogarty. They must be pretty well done with all their buildings out there now.

Dr. Masland. We have a training program in neurology which is based at that hospital under Dr. Sanchez Longo.

Mr. Fogarty. The new hospital?

Dr. MASLAND. Yes. We also have a very strong training program in ophthalmology in Puerto Rico, which has a very nice relationship with the Latin Americans. They are sending people there for training.

Mr. FOGARTY. That is good.

(The special report referred to follows:)

SPECIAL REPORT: LABORATORY OF PERINATAL PHYSIOLOGY IN PUERTO RICO

A major research center in the Western Hemisphere where primate studies are increasing knowledge of the perinatal causes of cerebral palsy, mental retardation, and other developmental neurosensory disabilities, is the Institute's Laboratory of Perinatal Physiology, in San Juan, P.R. A colony of more than 900 Rhesus monkeys comprise the total population of this unusual facility where scientists study factors operating at or before birth to produce brain damage.

Scientific investigations in Puerto Rico of harmful factors that produce injury to newborn monkeys complement efforts of the Institute's multi-institutional collaborative perinatal project involving the study of 50,000 mothers and their offsprings. It is important that this massive clinical investigation program to ascertain causes of neurosensory disturbances of infants and children be accompanied by experimental animal studies to permit a full utilization of leads from animal to man. Studies by scientists in Puerto Rico have helped clarify the mechanism responsible for damage to the brain in the critical perinatal period, from conception to soon after birth, which are being observed in patients in the collaborative project.

Before the Puerto Rican program started in 1956, scientists had demonstrated that brain damage associated with mental retardation could be induced in guinea pigs by partial asphyxiation at birth. The same procedure was followed with monkeys in the Puerto Rican facility. An experimental technique was developed in which the unborn monkey was delivered by caesarean section and asphyxiated. Then the baby monkeys were resuscitated by inflating their lungs with oxygen.

Infant monkeys subjected to such controlled asphyxia and resuscitation show varying degrees of neuromotor and behavioral handicaps. These studies strongly indicated that interference with maternal circulation at birth, either because of oxygen deprivation (anoxia) or accumulation of metabolites (toxins), or both, will cause damage to the brain of infant monkeys and bring about clinical syndromes resembling cerebral palsy, mental retardation, epilepsy, and deafness. The most characteristic cerebral palsy syndrome seen in the baby monkey closely resembles that of human kernicterus.

After establishing that anoxia occurring near the end of the gestational period can cause permanent damage in the primate brain, laboratory scientists found that much of the brain damage which results from oxygen lack occurs during a chain of events, continuing several days after asphyxia, and not actually during the time the infant is suffocating. If a method can be found to interrupt this process, it may be possible to reverse the deleterious effects of asphyxia.

Evidence has accumulated in recent years to indicate that certain changes in the blood caused by oxygen deprivation could be minimized and damage lessened by intravenous injections of glucose and alkali. Further research studies this past year confirm the value of this treatment, which could have important implications in preventing certain forms of cerebral palsy and mental retardation.

Another important area under study concerns the effect of uterine contraction on the infant's head. Findings regarding the effect of deviations of uterine motility on the infant's health underscore the need for caution in the use of certain drugs which induce delivery, because of the danger that sustained contraction of the uterus may result in injury to the child's nervous system.

Animals from the Puerto Rican colony are also playing a role in studies of German measles and its effect during pregnancy.

The monkey population consists of 450 free-ranging monkeys living on the island of Cayo Santiago, off the southeast coast of Puerto Rico, 42 miles from San Juan; 150 monkeys, free ranging and in compounds, added this past year to the islands of Isla Cueva and Isla Guayacan; and a colony of about 350 caged animals located at the University of Puerto Rico's School of Medicine, with adjacent laboratory facilities.

Comparisons between the free-ranging and caged colonies are being made of the physical and neurological development of those animals of known age and state of health. These studies provide a valuable baseline for observing deviations of development imposed by the experimental environment.

Funds were appropriated in fiscal year 1963 to build a new facility in Puerto Rico, to provide additional space for conducting fundamental animal research, chiefly on primates. The program of requirements has been prepared and is in process of review before employing an architect-engineer for final design. These added facilities will make it possible to expand studies of problems of development, growth, and maturation of the nervous system, and to observe those factors which may cause or lead to neurological and sensory disorders of infancy and childhood.

GERMAN MEASLES

Mr. LESINSKI. Doctor, you say that German measles contracted by a mother while carrying would cause cerebral palsy of an unborn child?

Dr. MASLAND. Yes, sir.

Mr. LESINSKI. German measles also has other effects, besides that, do they not?

Dr. MASLAND. Fortunately, German measles is one of the mildest of childhood diseases, except in less advanced populations. In the isolated, primitive populations, the mortality rate from German measles is very high, but in the Western populations it leaves very little damage, and it is only the discovery of this effect on the unborn baby that has given us a new respect for this disease.

Mr. LESINSKI. In other words, would you suggest if there were German measles in a family, that the whole family get it, and let it go at that?

Dr. MASLAND. This has been recommended, yes.

EFFORTS OF DEPARTMENT TO INTEREST STUDENTS IN NIH EMPLOYMENT

Mr. LESINSKI. One thing bothered me. All of you testified to this. We have consistently allowed funds for the training of new personnel. I think that is only proper and fair with the new program; but what have all of you done collectively, not as individuals, but as a group to interest students in various colleges and universities and even in high schools, of the advantages available in the Federal Government?

What incentive have you given them?

Dr. MASLAND. Mr. Lesinski, you have raised a question which is of serious concern to us. If we are going to have adequate scientists for biomedical research in the future, they must be interested at the high school and college level.

Now, some of the voluntary agencies with whom we have had relations have developed a moving picture film on the nervous system which is designed for college students but which also is valuable for some of these younger groups, but we do not have—as far as the Institute is concerned—a responsibility or a mandate to provide this sort of orientation at the high school level.

Dr. Price, maybe you would wish to comment on this.

Dr. PRICE. The thing I wanted to comment on, really, was twofold. One is that so far as Government agencies are concerned there should be a general understanding that we would devote our efforts primarily to the higher educational levels and not become involved in any work at the general college and high school level, with respect to interesting students in careers in the health field and health research. There are quite a number of things that have been done, more by other groups than by our Government agency groups.

One thing is a cooperative effort by a variety of voluntary agencies, called the health careers project, under which there are provided materials describing a variety of careers in the health field, requiring different amounts of training. These have been prepared and distributed to high school counselors, so that they would have available to them information just of this kind, to help their students know what course to follow and what kinds of opportunities there might be for them in this field.

Mr. LESINSKI. What you are saying is the same thing I had in mind. It is for all of the HEW, the various segments, to prepare a list of the possible vacancies—not necessarily vacancies but where there is a lack of trained personnel—and to build up a story surrounding the advantages of that subject that you might want to study. In other words, it is the student's choice—and circulate that amongst your schools and so forth, so the kids, while going to school, will choose. I can tell you right now, most kids that come out of high school do not know what they want to do.

Dr. PRICE. I am reminded of one other thing, which I think is of considerable value in interesting young people in careers in Government; careers of a variety of sorts. This is the summer employment which is available to them in the Government agencies, which gives them the opportunity, at an appropriate time in their training, to work alongside a more mature scientist or technician, and thereby they become interested in his work and want to emulate him in their educational process.

Mr. LESINSKI. That is very good. Thank you, Dr. Price.

Dr. MASLAND. This is one of the things I have tried to emphasize to the voluntary agencies in my conversations with them, and I think it is important to recognize the tremendous contribution that the voluntary agencies are making through this type of activity, which seems to be far more appropriate for them than it is for us. I think they are doing an extremely valuable job which is not adequately recognized.

Mr. LESINSKI. That is all, Mr. Chairman.

TRANSFER TO SURGEON GENERAL

Mr. DENTON. Doctor, I note on page 258 of your justification that $28,000 of the money was transfered to the Surgeon General's Office.

Mr. KELLY. This is related to the creation within the Surgeon General's Office of a servicewide organization to deal with the grants management operation and, when he appointed Dr. Ernest Allen as the grants officer for the service, it was funded by a transfer of funds from the various appropriations.

Mr. DENTON. Does every one of the categorical Institutes transfer money to the Surgeon General?

Mr. KELLY. They did this fiscal year 1964. In 1965, it is carried as part of the Surgeon General's appropriation.

Mr. DENTON. Do you know how much was transferred?

Mr. KELLY. I believe the total figure was $90,000.

STROKES

Mr. DENTON. You were talking about strokes. I have a friend who had a stroke. He said they operated on his chest or neck right away. He had no benefit from it at all, and I know another man—a very well-known person in my district—who told me he was very fortunate to be in a hospital with a broken leg at the time he had a stroke, because they got to him right away. He does have some bad effects from that.

Is that very effective—this operation for a stroke?

Dr. MASLAND. This is still in the process of evaluation. I think we will find eventually that certain types of cases are benefited and others are not.

Mr. DENTON. Depending on where the blood clot is?

Dr. MASLAND. Where it is and how long it has been there, and so on; but in some cases it has been very effective.

What happens is that the arteries in the neck become plugged. They can be cleaned out by surgically going through the chest, up into the neck.

PARKINSON'S DISEASE

Mr. DENTON. Now, I notice that you say that Parkinson's disease could be caused by virus infection and that, also, it is possible that multiple sclerosis can be caused by virus.

Dr. MASLAND. I think what we intended to say was that this question needs to be resolved. We know that certain forms of Parkinsonism can be caused by a virus but we do not know whether it all is; and multiple sclerosis might be. We'd like to be sure whether this is possibly the case.

Mr. DENTON. You do not have any evidence, but you think you have some grounds for the investigation?

Dr. MASLAND. The Russians claimed to have isolated a virus from a patient with multiple sclerosis. The British have two reports of a scrapielike virus—which is a disease of sheep—which they isolated from patients with multiple sclerosis.

We have established a small laboratory at Patuxent where animals may be kept for long periods of time for observation. We are injecting into those animals material from patients suffering from kuree, that disease in New Guinea which has a great many resemblances to this disease from sheep. We want to find out whether any of these human diseases are due to viruses.

Mr. DENTON. It is just in the investigation stage, that is all?

Dr. MASLAND. That is right; yes.

LABORATORY IN GUAM

Mr. DENTON. I was interested in your statement about the experiments in amyotrophic lateral sclerosis and your laboratory in Guam.

Dr. MASLAND. Yes.

Mr. DENTON. As I remember amyotrophic lateral sclerosis resembles multiple sclerosis?

Dr. MASLAND. That is right.

It is very similar in the type of paralysis, but probably the basic disease is different.

Mr. DENTON. This was traced, as I get it, to the Spaniards originally?

Dr. MASLAND. That was the original thought, that it was an inherited disease, but our most recent evidence strongly suggests that it is something in the environment.

Mr. DENTON. In those islands you had the natives, then you had the Spaniards, then the Germans, and then the Japanese, then the Americans. There is a great deal more blood there than just pure Samoan.

Dr. MASLAND. One thing that disturbs us very much is the discovery of a person from the United States, who has been living in Guam for quite a few years, who has the disease. We are almost certain now that it is not purely a hereditary disease. We are looking more intensively at the diet, the climate, and other factors that might be responsible.

Mr. DENTON. Where is your Laboratory in Guam?

Dr. MASLAND. In the Guam Memorial Hospital.

Mr. DENTON. Where is that?

Dr. MASLAND. In Agana.

Mr. DENTON. Did you make any tests out in the outer islands?

Dr. MASLAND. Yes. We have been traveling on those islands in order to do epidemological investigations.

Dr. DENTON. You are limited to the Mariana Islands, I take it?

Dr. MASLAND. No; we have also been on the Carolines. We have been on Saipan. There is a lot of it on Saipan.

Mr. DENTON. There are not a great many people there, now.

Dr. MASLAND. No; that is true.

Mr. DENTON. About 8,000.

Dr. MASLAND. That is right.

Mr. DENTON. About half are children.

Dr. MASLAND. Well, there is amyotrophic lateral sclerosis among the Carolinians and on Saipan.

REPUTATION OF THE INSTITUTE'S WORK

Mr. DENTON. I have a constituent who is very loud in Dr. Masland's praise. I spoke about this the other day. I am going to speak about it again. This young boy, I guess he is about 5 years old; his father had given him every kind of medical attention that he could have gotten. He had this boy every place. He had him in New York; he had him in Johns Hopkins; he had him everywhere for a cure for epilepsy, and he heard the only place where they could cure him was here at Bethesda. He brought the boy down here, and it was an unusual case and we arranged with Dr. Masland to take him out there as part of a research project. Within a week's time they had discovered the difficulty. It was a kidney defect; and the boy is perfectly well today. His father has to give him an injection every morning, I think. Outside of that, he leads a perfectly normal life.

Now, this was the only place in the world where they could get that discovery and, Dr. Masland, I think you should take great pleasure in your being able to carry on that kind of work. Every time I see this boy's father, he says, "The trouble with you people is you do not tell people enough of what they are doing in that Clinical Center." He said, "Few people know about it. You should sing their praises a little bit louder." He said, "I assure you, I am." I think he has told every druggist and doctor in my part of the country.

I think you should take great deal of pride in that particular case, Doctor.

Dr. Masland. Thank you.

Mr. Denton. We will adjourn until 10:30 tomorrow.

(The following was submitted later for the record:)

Mortality, Morbidity, and Cost of Disease

CANCER

Statistics of theannual number of deaths and total current number of disabilities caused by the major diseases dealt with in the National Cancer Institute, and the estimated annual cost to the Nation.

I. Cancer deaths in 1962 (unpublished data supplied by the national office of Vital Statistics Division)

Buccal cavity and pharynx	6,481
Digestive system	92,047
Respiratory	44,644
Breast	24,958
Genital organs	39,590
Urinary organs	13,299
Other sites	30,791
Leukemia	12,997
Lymphomas	13,755
Total, all sites	278,562

II. Cancer disability in 1962 (estimated on the basis of data supplied by the National Cancer Institute and the National Health Survey Division)

(*a*) Estimated cases under treatment	863,000
(*b*) Estimated person-days of disability (these estimates have a large margin of error):	
Restricted activity	54,000,000
Sick in bed	32,700,000

III. Cancer's cost to the Nation in 1962

(*a*) Hospital bill, $350 million (estimated by the American Cancer Society).

(*b*) Loss of income, $210 million (based on the American Cancer Society estimate of an annual loss of 50,000 man-years due to cancer illness and an average annual income of $4,200). This minimal estimate includes an allowance for loss of productivity due to retirement for cancer disability, but not the loss of potential productivity because of a cancer death during the working years.

(*c*) The economic effect of the loss of services of executives and skilled workers through cancer illness is difficult to calculate. Estimates based on the average annual contribution per member of the labor force (age 18–65) to the gross national product would indicate that cancer brings about a loss to society in goods and services valued at approximately $15 billion per year.

MENTAL ILLNESS

Statistics on the total current number of mentally ill persons receiving psychiatric care, by type of facility and estimated cost.

I. Estimated number of patients under care

Over 2 million persons received care for mental illness or mental deficiency in psychiatric facilities during 1962. This understates the numbers who received special care; not only are the figures for psychiatric facilities underreported, but some mentally ill persons are served at nonpsychiatric medical or custodial facilities or by private psychiatrists. In addition a large number of persons who are mentally ill or mentally deficient do not receive any type of treatment. Therefore, this is a minimum estimate of the numbers of patients who were mentally ill in the United States for 1962.

Number of patients receiving care during 1962 [1]

Type of facility:	
State and county mental hospitals	792, 635
Veterans' Administration hospitals	127, 193
Private mental hospitals	85, 266
General hospitals with psychiatric facilities	219, 006
Public institutions for the mentally deficient	184, 489
Private institutions for the mentally deficient	10, 036
Outpatient psychiatric clinics	[2] 741, 000
Total	2, 159, 625

[1] The number of patients receiving care is based on the sum of resident patients at beginning of year plus all admissions (excluding transfers).
[2] Includes VA clinics.

NOTE.—These data are based on reports received by the National Institute of Mental Health from State agencies, hospitals, and clinics.

II. Estimated annual cost to the Nation

To Federal, State, and local governments for care of patients, fiscal year 1963,[1] $1,853,004,000.

CARDIOVASCULAR DISEASES

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the National Heart Institute, and the estimated annual cost to the Nation.

I. Deaths from cardiovascular diseases during 1962 (Division of Vital Statistics, National Center for Health Statistics)

Category:	*Number*
Arteriosclerotic heart disease (includes coronary disease or "heart attacks")	527, 561
Cerebrovascular lesions (includes strokes and other blood vessel diseases in the brain)	197, 451
Hypertension	74, 673
Nonrheumatic chronic endocarditis and other heart muscle degeneration	54, 645
General arteriosclerosis	36, 848
Rheumatic fever and rheumatic heart disease	17, 751
Other cardiovascular diseases	48, 508
Total	957, 437

II. Disabilities from cardiovascular diseases (unpublished figures from Division of Health Interview Statistics, National Center for Health Statistics, based on data collected during the period July 1961 to June 1963)

	Disability category		
	Restricted activity	Bed disability	Work loss [1]
Average annual number of disability-days (in millions):			
Cardiovascular conditions	458	195	38. 7
Heart conditions	211	90	19. 8
High blood pressure [2]	66	25	4. 9
Average number of persons (in thousands):			
Cardiovascular conditions	[3] 1, 255	[3] 533	[4] 161
Heart conditions	579	245	82
High blood pressure [2]	182	68	20

[1] For persons currently employed.
[2] Without heart involvement.
[3] Disability days, 365.
[4] Disability days, 240.

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[1] Based on data received from Federal and State agencies. Data from private agencies and individuals are not available.

III. Estimated annual cost to the Nation (July 1963 Survey of Current Business, Office of Business Economics, Department of Commerce; unpublished data from Veterans' Administration and from National Center for Health Statistics)

Compensation and pension payments to veterans disabled by diseases of circulatory system totaled about $571 million in 1963. Lost productivity for 1962 of those still in the labor force (at estimated $5,000 average annual earnings) is estimated at $805 million. Figures on expenses of hospitalization and other medical care are not available, nor are figures on which to estimate the productivity loss of persons no longer in the labor force (retired for disability).

DENTAL DISEASES

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the Dental Institute, and the estimated annual cost to the Nation.

1. Deaths related to dental disease

No information available.

2. Disabilities caused by dental diseases

The oral diseases are rarely death-dealing or completely incapacitating, but they produce a notable amount of pain and disability because they are almost universally prevalent. Oral diseases constitute a major national (and international) health problem. They affect almost everyone, cause much suffering, and create dangers of chronic illness.

Dental caries is the most prevalent of all diseases in the United States. It affects more than 90 percent of the entire population. Periodontal disease is the most common of the oral diseases of adulthood. Half the population over the age of 50 and practically everybody over 60 suffers from this disease.

Disability is increased by the fact that a large proportion of these disorders remain untreated. Surveys show that half the children in the United States under the age of 15 have never been to a dentist and that large numbers of adults do not see a dentist even once a year. It is estimated that 700 million to 1 billion cavities in the United States are untreated.

Serious disabilities in speech, swallowing, hearing, physical appearance, and psychological adjustment afflict some 7,000 children born each year with cleft lip and palate.

3. Estimated annual cost to the Nation

Surveys by the Department of Commerce, the Bureau of Economic Research, and the Health Information Foundation indicate that the people of the United States spent from $2.2 to $2.5 billion in 1962 for professional dental care. This bill covers less than half the population and does not include the large untreated group or those receiving care from Government or philanthropic agencies. The amount is double that spent 10 years ago and seven times the amount spent in 1935; it represents 10 percent of the expenditures for health care of all types. Man-hours lost from productive work come to over 125 million a year (even if only 2 hours are lost per worker per year). There is also a direct relation between oral health and systemic conditions affecting the body as a whole, which influences the scope of this public health problem. Complicating factors are the shortage of dentists and the increasing cost of treatment. The role of research is important because research can provide a key to causes, develop improved methods of treatment and ultimately provide measures of prevention for oral diseases.

Though 10 percent of health expenditures are for dental care, less than 2 percent of health research expenditures are in the field of dental research.

ARTHRITIS AND METABOLIC DISEASES

Statistics concerning the annual number of deaths and total current number of disabilities caused by some of the major diseases under study in the National Institute of Arthritis and Metabolic Diseases and the estimated annual cost to the Nation.

I. Deaths during 1962 (National Office of Vital Statistics)

Category:	
Diabetes mellitus	31, 222
Gastrointestinal diseases (ulcer of stomach and duodenum, and cirrhosis of the liver)	35, 362
Total	66, 584

II. Disabilities (National Health Education Committee, Inc., 1962)

Rheumatic diseases (624,000 persons completely disabled and 3 million persons partially disabled), 3,624,000.

III. Estimated annual economic cost to the Nation (National Health Education Committee, Inc., 1963)

Rheumatic diseases (arthritis, rheumatism, gout), $2 billion.

ALLERGIC AND INFECTIOUS DISEASES

Statistics of the annual number of deaths and total current number of disported illnesses caused by selected diseases dealt with in the National Institute of Allergy and Infectious Diseases and the estimated annual cost to the Nation are presented in tables I, II, and III.

Deaths attributable to allergic, infectious, and parasitic diseases during 1961 are used as the National Office of Vital Statistics advises that only preliminary data are available for more recent years.

The following tables report only those deaths and cases which are diagnosed by a reporting laboratory or a qualified physician. health officer, or other professional person.

TABLE I.—*Mortality*

Category	*Reported deaths, 1961*
Infectious and parasitic diseases:	
Bacterial diseases:	
Streptococcal sore throat and scarlet fever	130
Septicemia and pyemia	[1] 1, 886
Tuberculosis	9, 938
Venereal diseases:	
Syphilis	2, 850
Gonorrhea	19
Other	11
Pertussis (whooping cough)	76
Viral diseases:	
Acute upper respiratory infections (includes "common cold")	808
Influenza	2, 137
Hepatitis	976
Measles	434
Poliomyelitis	90
Unspecified bacterial and viral diseases:	
Bronchitis, acute	[1] 1, 031
Dysentery, all types	[1] 547
Meningitis, all types	[1] 2, 849
Pneumonia, all types	[1] 56, 579
Other bacterial and viral diseases	[1] 5, 669
Fungal infections: All types	[1] 375
Parasitic diseases:	
Amaebiasis and other protozoal diseases	85
Worm infestation	58
Total reported	86, 548

[1] Incomplete data. Figures given represent only a small portion of the deaths attributable to these diseases.

Since most of the listed conditions cause illness rather than death, morbidity for 1962 is presented in table II to reflect the extent of impairment created by these diseases.

TABLE II.—*Morbidity*

Category	*Reported cases, 1962*
Allergic diseases:	
Asthma and hay fever	[1] 1,009
Other allergic diseases	([2])
Infectious and parasitic diseases:	
Bacterial diseases:	
Streptococcal sore throat and scarlet fever	315,809
Septicemia and pyemia	([2])
Tuberculosis	53,788
Venereal diseases:	
Syphilis	126,245
Gonorrhea	263,708
Other	2,141
Pertussis (whooping cough)	17,749
Viral diseases:	
Acute upper respiratory infections (includes influenza, acute bronchitis, all types pneumonia and the "common cold")	148,010,000
Hepatitis	53,016
Measles	481,530
Poliomyelitis	910
Unspecified bacterial and viral diseases:	
Dysentery, all types	[1] 13,334
Meningitis, all types	[1] 4,033
Other bacterial and viral diseases	[1] 153,814
Fungal infections: All types	([2])
Parasitic diseases:	
Amaebiasis	3,057
Worm infestation	[1] 8,636
Total reported	149,508,779

[1] Incomplete data. Figures given represent only a small portion of the cases attributable to these diseases.

[2] Data not available. These categories are non-notifiable acute diseases and are not reported or are reported so irregularly or infrequently that inclusion in the table would be meaningless.

Table III presents the days of disability per year and per 100 persons and the cost to the Nation for the allergic, infectious, and parasitic diseases for 1961. Figures for annual cost to the Nation include only the value of time lost from work due to disability. Statistics are not available to include the cost of medical and hospital care, drugs, and compensation specifically attributable to these diseases.

TABLE III.—*Days of disability per year and per 100 persons, and cost to the Nation, 1961*

Item	Acute condition group		Cost to the Nation
	Infectious and parasitic	Respiratory	
Number of cases	49, 100, 000	196, 300, 000	
Rate per 100 persons	27. 6	110. 3	
Total disability days: [1]			
Restricted activity	225, 400, 000	631, 400, 000	(2)
Bed disability	107, 700, 000	267, 900, 000	(2)
Work loss	16, 000, 000	68, 000, 000	$1, 680, 000, 000
School loss	46, 800, 000	84, 900, 000	(2)
Days per 100 persons: [1]			
Restricted activity	126. 6	354. 7	
Bed disability	60. 5	150. 5	
Work loss	25. 7	109. 6	
School loss	121. 7	220. 6	

[1] Definition of terms:

Restricted activity: A day when a person cuts down on his usual activities for the whole of the day because of an illness. Includes bed-disability, work-loss, and a school-loss days.

Bed disability: A day on which a person was kept in bed either all or most of the day because of an illness. Includes those work-loss or school-loss days actually spent in bed.

Work loss: A day on which a person loses the entire day because of an illness. Computed for persons 17 years of age and over.

School loss: A day on which a child loses the entire schoolday because of an illness. Computed for children 6 to 16 years of age.

[2] Data not available.

NEUROLOGICAL DISORDERS

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases handled by the National Institute of Neurological Diseases and Blindness, and the estimated annual cost to the Nation.

I. Deaths from neurological ailments during 1962

Category [1]	*Number*
Cerebral palsy	1, 328
Cerebrovascular diseases (includes strokes and related brain ailments)	197, 451
Parkinson's disease (paralysis agitans)	2, 816
Multiple sclerosis	1, 487
Muscular dystrophy and related ailments	555
Epilepsy	2, 048
Myasthenia gravis	237
Amyotrophic lateral sclerosis	1, 164
Encephalitis	484
Brain tumors	7, 450
Spina bifida and meningocele	1, 511
Total, by reportable categories [1]	216, 531

[1] The approximately 200 different neurological ailments pose unusual statistical problems. The cerebral palsy figure above includes categories 351 and 352 of the International Classification of Diseases but not the cases found in the undifferentiated "other" category number, 334. Mental retardation, blindness, deafness, and speech disorders are major neurological and sensory problems, but are not causes of death. Even in ailments for which deaths are reported, figures are unreliable because the chronically ill patient, weakened by disease, may die from an intercurrent infection and the death certificate may not record the basic neurological illness.

NOTE.—This is about 12.3 percent of the total U.S. deaths in 1962 of 1,756,720.

Source: U.S. National Vital Statistics Division.

II. Disabilities from neurological diseases

The Division of Health Interviews Statistics of the U.S. National Center for Health Statistics estimates, from home interviews, that 322,000 persons consistently suffer some limitation in living because of headache or migraine. About 1,144,000 persons whose corrected vision is not sufficient to read newsprint are handicapped by this impairment in daily living.

As the Division of Health Interview Statistics does not have figures on disabilities from specific neurological diseases, this Institute uses morbidity estimates from the respective voluntary associations. These statistics come from known experience with cases or from surveys of given areas. Some neurological patients, such as those with epilepsy, conceal their impairment to avoid job discrimination.

Disability and current number of disabled persons

Category	*Total (estimated)*
Cerebral palsy	550,000.
Mental retardation (3 percent of the poplation; 126,000 born annually).	5,400,000.
Cerebrovascular diseases	Between 1,000,000 and 1,800,000.
Parkinson's disease	300,000 to 500,000.
Sclerosing disorders:	
Multiple sclerosis	250,000.
Other demyelinating diseases	250,000.
Muscular dystrophy	200,000
Epilepsy	1,000,000.
Myasthenia gravis	30,000.
Amyotropic lateral sclerosis	30, 000.
Infectious neurological disorders (including encephalitis).	Over 1,000,000.
Brain tumors	Over 500,000.
Disorders of vision:	
Legally blind	399,300.
Partially seeing	2,048,700.
Disorders of hearing, totally deaf	125,000.
Speech defects interfering with normal development.	5 percent of schoolchildren.
Speech defects	3 percent of adult population.

III. Estimated annual cost to the Nation

The estimated of neurologically disabled persons, excluding duplications for those with multiple disorders, is more than 10 million. Of these, approximately one-third are totally disabled. It has been estimated that the cost of care for the totally disabled and for a significant number of the partially disabled is more than $5½ billion. Lost productivity to the Nation caused by these disorders may be more than $20 billion.

During calendar year 1963, social security disability benefits of $92 million were paid to 166,000 beneficiaries whose disabilities had begun in childhood. Of these disabled beneficiaries, more than 90 percent had neurological disabilities.

In fiscal year 1963, the Veterans' Administration sent $428 million in compensation checks to 391,285 veterans for service-connected disabilities, either psychiatric or neurological.

The annual cost to the States of the 195,000 mentally retarded persons in State institutions is estimated at $250 million. No one knows the cost of supporting those in private institutions. Less than 4 percent of the 5 million mentally retarded are in institutions, public or private; the cost to individual families and communities for the other 96 percent is not known. It is estimated, however, that the total cost of care of the mentally retarded is more than $1 billion a year.

RESEARCH HIGHLIGHTS OF THE NATIONAL INSTITUTES OF HEALTH

INTRODUCTION

Since man first found the means for communicating with succeeding generations, he has left a record of how he has applied his imagination and intellect to problems affecting daily life. The chief of these related to survival. Through the centuries, however, these survival problems have changed from those concerning the hazards of living with and attaining superiority over other animals of greater strength, size, and often, greater lifespan, to the control of other, often more subtle hazards in his environment.

History is rich with accounts of man's achievements that range in subject matter from astronomy through xylography and in time from the stone age to the nuclear and space age. One fact emerges: that man has been far more successful in unraveling the mysteries of his physical environment than he has been in developing an understanding of the basic life processes that take place within his own body. He has emerged from the cave to startling heights in architecture, and he has refined his knowledge of inertia and related physical phenomena from the inclined plane and the wheel to a partial conquest of gravity itself. These are problems that man has been pondering on a wide scale, literally for centuries.

The results are highly visible and consequently relatively easy to comprehend. The exploration for new knowledge in the biomedical sciences, on the other hand, is a relatively recent development when one considers the effort in the perspective of man's total history. As recently as the 18th century, the lifeblood of a President of the United States was drained from his body as a treatment for fever. In the late 19th century, those who suggested a relationship between the mosquito and the spread of yellow fever were openly scoffed. In World War I many more American lives were lost from disease than from enemy bullets.

Then, less than 20 years ago, the first full-scale analysis of what could be done to mount a concerted attack on all of the major health problems was prepared and made public. Thus when the National Institute of Health, as it was then called, was given responsibility for development of a national medical research program in 1946, it was being asked to lead an attack on a wide range of health problems that had been accumulating for centuries.

At that time it was clear that a lack of fundamental knowledge concerning the nature of disease and underlying life processes blocked further progress in the control of the major health problems. For example, new knowledge was needed that would provide the techniques and concepts for developing the then infant science of virology and for understanding the genetic abnormalities manifesting themselves in metabolic disorders and neurological defects. It was also clear that no Federal laboratory could mobilize the diverse scientific skills or develop the size of program needed. The successful pattern of Federal support for university centered technological research during World War II served as a background for the decision to join with the Nation's non-Federal institutions—universities, medical schools, hospitals, and independent research laboratories—to improve the Nation's health.

In the years that have followed that time of decision, NIH has strengthened its own capacity for doing medical research, fostered training programs to increase the Nation's pool of biomedical research manpower, and has administered programs in support of unprecedented numbers of research projects in non-Federal institutions throughout the country. NIH is the instrument of the U.S. Department of Health, Education, and Welfare's Public Health Service through which the Congress makes available funds for the conduct and support of medical research. As such, it is today the largest single source of support for medical research in the Nation.

Although a steady stream of new scientific findings has been flowing from the NIH laboratories and the hundreds of medical schools, hospitals, and independent research laboratories it supports, the most exciting developments in the attack on disease are still in the future. It is predictable that just as surely as today's major disease problems have entrenched themselves as a part of our daily lives, they will be forced out of our pattern of life by the new knowledge that is now emerging from laboratories and clinics throughout the world.

This publication is not intended as an exhaustive account of every research activity at NIH, nor are the examples necessarily the most significant. It has been prepared in response to an expression of concern on the part of Congress that practitioners, as well as the general public, should have a greater opportunity to be aware of research activities and accomplishments made possible by public funds.

The following pages describe illustrative areas of interesting and encouraging research now underway. This work—research for health—will progress not so much in spectacular breakthroughs as it will in the painstaking step-by-step addition of new knowledge. This knowledge, when translated into better methods of treatment, improved procedures and tests, new drugs, and better health practices in the home, will add years of productivity and happiness to our lives.

NATIONAL CANCER INSTITUTE

INTRODUCTION

Cancer research is almost as diversified as the complex of diseases the term "cancer" covers. Investigations of the causes of cancer penetrate the innermost recesses of the body's cells and embrace the air man breathes, the food he eats, the occupations he pursues. The search for treatment has yielded powerful X-ray machines. the extraction of drugs from common plants, ingenious procedures to make cancer surgery more effective.

Research programs reflecting this diversity are carried out in the laboratories of the National Cancer Institute, with the cooperation of cancer patients at the National Institutes of Health's Clinical Center, and in the many institutions across the country and around the world where cancer research is supported by Public Health Service grants. Knowledge is accumulating. One day this knowledge and that still to come will bring about control of the Nation's No. 2 killer.

For members of those two out of every three American families struck by cancer each year, progress understandably seems slow. But the present ratio of 1 out of 3 Americans now being saved from cancer bears witness to progress made since the National Cancer Institute was established in 1937. At that time, the ratio was less than 1 out of 5. And in leukemia, a form of cancer still invariably fatal, research has given more than a year of nearly normal life to children once doomed to die within weeks.

Though the paths of cancer research are varied, its goals are few and simply stated. Scientists hope to find out what causes cancer and how it can be prevented. If not prevented, they want to find better ways of diagnosing the disease early and treating it effectively.

CAUSATION

Research leads in cancer causation have been particularly exciting during the past year. Studies of viruses, environmental factors, and certain chemicals are beginning to cross and overlap. Many experts believe these will ultimately merge in a highly-refined study in depth of human cancer causation.

To date, no human cancer-causing virus has been found, although evidence accumulated over a number of years has demonstrated that viruses cause many forms of cancer in animals. A National Cancer Institute scientist has reported isolation of yet another virus that causes leukemia in mice. This newest virus in only 7 days causes a nonleukemic disease which progresses to leukemia in 30 days.

As far as is known, animal tumor viruses cause the disease only in animals. However, a monkey virus that causes tumors in laboratory animals was recently shown to bring about bizarre, malignant-like changes in human cells growing in tissue culture. On the other side of the coin, so to speak, two of a group of viruses which cause acute respiratory illness in man have been found capable of producing tumors in newborn hamsters.

Research has shown that viruses, although they do cause animal cancer, can be tamed, thus taking the terror out of the possibility that some forms of human cancer, too, may be of viral origin. Two Institute scientists found during the past year that a vaccine made from a weakened strain of a normally highly active tumor virus protected animals from the tumor-producing effects of the virulent strain. This is the latest in a series of experiments by various investigators which may eventually show how to prevent some cancers in man.

Protection against cancer could also grow out of a better understanding of how tumor viruses bring about a malignant change for, if this were known, some means of interrupting or reversing the process might be developed. The electron microscope, with its powerful magnification, is beginning to reveal some of the secrets of viruses. Using this instrument, two members of the Institute staff found last year that three animal leukemia viruses have tails and hexagonal heads, a shape not unlike that of bacterial viruses. This tell-tale shape makes it easier for scientists to spot these leukemia viruses quickly.

To pursue all such leads as vigorously as possible, the National Cancer Institute recently organized a special task force of staff and other scientists active in human cancer virus research, which, working together, hopes within several years to obtain evidence in support of a viral cause of at least one type of cancer, possibly leukemia.

The Institute has also assumed the lead in developing such necessary research resources as virus-defined animals and virus-free cell lines. These "clean" systems are as necessary for the virologist as spotless test-tubes and purified substances are for the chemist. To date, 14 cell lines have been characterized and placed in a cell bank on which qualified investigators can draw for seed stock. Commercial supplies of germ-free and virus-defined mice have been increased through Institute efforts, and germ-free chickens and small primates (marmosets) are being evaluated for usefulness in virus-cancer research.

Another approach to cancer causation is that taken by scientists testing cancer-causing chemicals in the environment. These members of the Institute staff are trying to determine whether a minimum cancer-causing dosage level exists for such agents in animals and in man.

Epidemiological investigations of Institute scientists, in collaboration with scientists in other parts of the Nation and, indeed, in the world, are recording statistical changes in cancer risks for individuals or groups who move from one environment to another. For example, an Institute scientist has reported that smokers who move frequently from one community to another are more likely to develop lung cancer than less mobile citizens and that the risk is greatest for heavy smokers moving from rural to metropolitan areas and for the foreign-born settling in large cities. A comparative study is being made of the relationship of customs and personal practices to the incidence of cancer of the lung and stomach among the Japanese in Japan, Hawaii, and California. A similar study of factors influencing the cancer risk for people who migrate from Poland to the United States is being developed with the Polish Ministry of Health and the National Cancer Institute of Poland.

DIAGNOSIS

Diagnostic research has yielded new investigative leads. One such is the complex X-ray procedure, mammography, which is being studied for its value in diagnosing early breast cancer. To determine whether mammography can lower the death rate for breast cancer, which has remained virtually unchanged for 30 years, the Institute has awarded a contract to a large health insurance company to plan a 10-year study that will compare the results of treatment in large numbers of women whose breast cancers were detected through mammography with the outcome for those diagnosed by other means.

TREATMENT

Surgery and radiation are the principal methods of treating cancer, and, each year, improvements in these techniques save more lives. But many experts believe that in drug therapy research lies the hope of the future.

This hope has already been borne out in leukemia: although no cures have been effected, drugs dispel symptoms for long periods and prolong lives where surgery and radiation can offer nothing. Fifteen years ago, acute leukemia patients almost always died within 12 to 16 weeks after diagnosis. Gradually, two drugs, plus cortisone and related steroids, came into general use as they kept many patients with acute leukemia alive for more than a year.

Just recently even this record has been improved through new and dramatic developments. The National Cancer Institute has played an important part in these advances.

Three new drugs have been added to the three already found useful in treating leukemia. There is hope now that with the increased number of drugs, physicians can find a combination that will result in longer and longer periods of remission, and evenutally complete control.

Supportive treatment which keeps leukemia patients alive long enough for drug treatment to take effect now includes the use of a special technique worked out by Institute scientists to provide blood platelet transfusions to those patients in danger of hemmorrhage, and white blood cell transfusions to those fighting bacterial infections.

Thus encouraged, the Institute has organized another task force of Federal and non-Federal scientists to seek long-term control of acute leukemia and to make existing therapy available to an increased number of patients.

The search for new and better drugs for treating cancer was organized on a national, cooperative basis 7 years ago by the National Cancer Institute. Since then, more than 70,000 synthetic chemicals and 100,000 natural products have been tested for antitumor activity in laboratory animals. The number of substances to be screened annually has been reduced, and the number of test systems increased to about 20 tumors in mice, rats, and hamsters instead of the 3 tumors used formerly. Though it is not possible to test every new substance in every tumor, the expanded, more flexible screen hopefully will pick out drugs with activity against common solid tumors, such as cancers of the lung, colon, and pancreas, in which, to date, drug treatment is only occasionally beneficial.

New projects only recently added to the cancer chemotherapy program administered by the Institute include the development of methods to test substances for antiviral activity. This move is based on the assumption that viruses will one day be proved to cause some forms of human cancer and drugs will be needed that are effective against these agents. Another screen under development is one to find chemicals that will modify the effects of radiation therapy. These may either protect normal tissues or may concentrate in cancerous tissue and make more effective the ordinary radiation dose.

OTHER ACTIVITIES

Not all of the research activities of the National Cancer Institute are located on the National Institutes of Health campus near Washington or even in this country. In Ghana, the National Institutes of Health's West Africa Research Laboratory has been placed in operation with specific administration of the Laboratory delegated to the National Cancer Institute.

Here, in one of Africa's newest nations, a collaborative program of research on health problems of concern to all peoples is being developed. The Ghanaian Government is providing laboratory and clinical space, facilities, and housing while the U.S. Government is providing professional and technical staff, equipment, and supplies.

Ghana offers many unusual opportunities for the study of diseases that are rarely seen in unmodified form in the United States. It also presents a cross section of the cancer problem in Africa south of the Sahara and is in the region that apparently has a high incidence of an unusual lymphoma.

CONCLUSION

Current cancer research not only takes many paths but does so in many countries. The worldwide effort to gain and utilize the knowledge that will wipe out malignant disease is one which the National Cancer Institute shares with many other research institutions. As the U.S. Government's principal agency for the study and control of cancer, the Institute takes pride in the quality of the work of its own scientists, shares in the accomplishments of its grantees, and plays a major role in stimulating the development everywhere of new ways to fight an old enemy.

NATIONAL HEART INSTITUTE

PERSPECTIVE

Basic studies brought new knowledge about the structure, function, and abnormalities of the heart and circulatory system.

Many advances were recorded in clinically useful research, in improvements in diagnosis, treatment with therapeutic agents, and heart and blood vessel surgery.

Heart training grants and fellowships helped add to the short supplies of trained manpower and to maintain the rate of progress in heart research.

The statistical picture of heart disease—a complex of over 20 diseases of the heart and blood vessels—showed both a bright and a dark side.

A decline continued for some kinds of heart disease. In middle-aged men (45 to 60), there has been a 6-percent drop in the death rate from strokes—damage in the brain's blood vessels—over about the past 10 years.

Death rates from three other kinds of heart disease showed even greater decreases: rheumatic fever and chronic rheumatic heart disease, 28 percent; nonrheumatic chronic endocarditis and other myocardial degeneration, 38 percent; and hypertension, with or without heart involvement, 33 percent.

These were important gains, reflecting progress. The whole statistical picture, however, showed that the total number of deaths from heart disease each year is still growing. In 1962, there were some 947,000 deaths—an increase of nearly 26,000 over 1961. This results largely from the general aging of the population and the upward trend in mortality from arteriosclerotic heart disease—which includes "heart attacks." The death rate here has increased 22 percent, from 226 per 100,000 population in 1952 to 275 in 1961.

This glance at the most recent year for which statistics are available, indicates the size, complexity, and nature of the problem or heart disease—and that a broad gaged research attack, commensurate with the needs, is achieving progress.

A further look shows how the Institute participated as a partner in the Nation's overall endeavor against heart disease.

TRAINING PROGRAMS

The National Heart Institute supported over 800 fellowships, training grants, and research career awards. These were made through the Heart Institute's program which provides for the training of qualified persons for research and academic careers in basic and clinical sciences related to cardiovascular health and disease.

The training grants and research fellowships programs of NHI are helping substantially to add to the Nation's resources for heart research. These programs, year by year, demonstrate that they are an indispensable component of the Institute's activities—one without which continuing progress in heart research itself could not be attained.

RESEARCH PROGRAMS

National Heart Institute research seeks new knowledge about the structure, function, and abnormalities of the cardiovascular system. Closely associated studies are concerned with application of fundamental knowledge to diagnosis, prevention, and treatment of diseases of the heart and blood vessels.

The National Heart Institute's research grants program supported more than 2,000 studies—ranging from specific, individual projects to collaborative and cooperative investigations by groups of scientists—in over 300 universities and hospitals throughout the Nation and abroad.

Research by NHI scientists and grantees contributed to knowledge of the cardiovascular system and its functions in health and disease, and to improved diagnosis, treatment, and prevention of certain cardiovascular disorders.

The range and kind of heart research progress are reflected in this sampling of areas in which these contributions occurred.

AREAS OF PROGRESS

Epidemiology

Epidemiology is concerned with the study of circumstances under which a disease develops or flourishes. These include factors within the host or his environment which interact to make him susceptible or resistant to the disease.

Epidemiological studies have forged strong links between the development of atherosclerosis and coronary heart disease and such factors as age; sex; diet; obesity; metabolic disorders, such as hypothyroidism, hypercholesterolemia, and diabetes; elevated blood pressure; cigarette smoking; occupation and degree of physical activity; psychic stress; and geographical location.

The Framingham study.—The Framingham study of the NHI represents the "microscopic" approach in epidemiological studies of coronary heart disease. This involves intensive study of a relatively small group to detect within-group differences in the incidence of the disease and to discover factors within the host or his environment that appear responsible for these differences. These risk factors and their relative importance in the development of coronary heart disease are then assessed in long-term studies on subjects initially free of the disease. The aim is to determine whether the presence of one or more of these factors in members of the population significantly affects subsequent development of the disease in these members.

Carefully controlled studies on 5,128 adults, found free of heart disease at initial examination and followed for periods of 8 to 12 years, indicate that the following factors are important determinants of susceptibility to heart disease:

Age and sex.
Elevated serum cholesterol.
Elevated blood pressure.
Electrocardiograph (EKG) changes.
Cigarette smoking.
Obesity.

The risk of developing coronary heart disease may be greatly increased in individuals with combinations of the above risk factors. Although, fortunately, few individuals have all of these factors working against them, but a goodly number may have combinations of two or more. A combination of only three—elevated blood pressure, elevated serum cholesterol, and EKG abnormalities—may increase an individual's risk by a factor of 25. Fortunately, many of the risk factors can be eliminated or reduced with the aid of the physician.

Dietary factors.—Since epidemiological studies have provided a mass of statistical evidence linking the kinds and amounts of fat in the diet to elevated serum cholesterol levels, it has been theorized that it might well be possible to bring about a significant reduction in mortality from heart disease through modifications in the dietary pattern. However, to prove or disprove this attractive hypothesis would require long-term population studies on a scale never before attempted.

With NHI grant support, a committee of experts has studied the many problems inherent in a massive undertaking of this sort. These investigators have concluded that before long-term, large-scale population studies can be undertaken with any success, the feasibility of such studies should be carefully tested.

Feasibility testing is now underway by means of a series of short-term studies in small population groups, composed mainly of free-living, middle-aged American males. Each group, consisting of about 225 men, is evenly divided into three populations and fed three separate diets. These diets differ in content of saturated, polyunsaturated, and total fat calories. The investigators will carry out various clinical and biochemical studies to evaluate the effects of these diets on certain factors associated with increased coronary disease risk and also on the development of the disease itself.

Occupation and degree of physical activity.—The results of many epidemiological studies indicate that heart disease is more prevalent among workers engaged in sedentary jobs than in those whose jobs entail moderate or marked physical exertion. Further support for this concept has come from studies on incidence of heart attacks over a 10-year period among 8,500 middle-aged workers in Israeli cooperative settlements. In these settlements, all members live in absolute equality with respect to housing, nutrition, and other environmental factors, irrespective of the nature or status of work performed.

The study showed that heart attacks were three times as common among the sedentary workers of these settlements as among those engaged in light or heavy manual labor. Other evidence collected by the same research team suggests that not only does physical labor confer some measure of protection against heart disease, but it also appears to exert a favorable effect on both immediate and long-term survival after first heart attacks.

In brief.—Epidemiology has been called the major discipline of preventive medicine; in our present state of knowledge, prevention of first heart attacks holds forth the greatest hope for reducing our appalling mortality from coronary heart disease. Although therapeutic advances have increased survival rates among its victims, about 17 percent of hospitalized patients still succumb during the acute stages. Because of the high proportion of sudden and unexpected deaths, many coronary victims never reach the hospital. In the population at large, data from the Framingham study indicate, death rates from first heart attacks may run as high as 34 percent.

Epidemiological evidence, by identifying factors predisposing to the development of coronary heart disease, may make it possible for physicians to identify highly susceptible individuals long before the disease produces clinical signs, and possibly before it can gain any substantial foothold. Many of these predisposing factors can be ameliorated or corrected; thus the physician is able to initiate measures to postpone the onset of coronary heart disease, or perhaps prevent it altogether.

Cholesterol research

A large body of evidence has been amassed linking elevated cholesterol levels in the blood to the development of the artery-clogging lesions of atherosclerosis, which cause most heart attacks. There is also abundant evidence that the amounts and kinds of fats in the diet are important determinants of blood cholesterol levels.

Cholesterol, source of this concern, is a tasteless, odorless, white, fatty alcohol found in all animal fats and oils, in egg yolks, and in milk and milk products. It plays a vital role—one that cannot be dispensed with—in many facets of body metabolism. The problem of reducing it and maintaining it at a "normal" level has spurred research seeking safe, effective, and practical means for this.

What are "normal" levels?

Nobody is sure, but most investigators agree that blood cholesterol levels considered normal in Americans are probably too high. How low should levels be pushed?

Again, nobody is sure, but many investigators feel that the lower the level, the better. Theoretically, health might be endangered by levels too low. However, given the serum cholesterol levels of most Americans and the limitations of currently available techniques for lowering cholesterol, this does not appear likely to pose much of a problem.

The most widely used therapeutic approach to control has been dietary modifications. Research in this field is continuing along many lines, with a major development being the beginning of a group of cooperative studies (mentioned above in epidemiology) to test the feasibility of some dietary methods and their effectiveness.

Another approach to blood cholesterol control involves a number of agents that inhibit cholesterol absorption or synthesis or affect its transport. Some appear promising, and more information on their actions and effects has been gained, but much more research must be done.

It remains to be proved whether reducing serum cholesterol levels will be of any benefit in preventing or retarding the development of heart disease. The approach, however, appears at this time to be the most promising one currently available, and must be pursued.

New drug for hypertension

A highly potent and effective new drug for lowering blood pressure was developed with NHI scientists playing a key role. Clinically tested and licensed for physician use, its performance has been particularly impressive in patients with severe hypertension, including those suffering malignant hypertension. Its potency, especially when used in conjunction with diuretic therapy, and its smoothness of action and relative freedom from serious toxic side effects, appear to make it the drug of choice for many hypertensive patients.

The new drug—alpha-methyl DOPA (Aldomet, Merck, Sharp & Dohme)—was synthesized by the company in 1953. For several years it was of interest only as a research tool for studies on amine metabolism; it demonstrated no effect on blood pressure in animals.

In 1958, NHI scientists became interested in the compound, since they felt it might be useful for pheochromocytoma or malignant carcinoid. The pharmaceutical company supplied the compound to NHI. Cautious testing of the drug in some patients with hypertension, and parallel biochemical studies in several patients with pheochromocytoma or malignant carcinoid, proved alpha-methyl DOPA remarkably effective for the hypertensive cases. Thus was introduced a new drug for high blood pressure.

Further clinical evaluation at NHI, along with basic biochemical studies to learn the drug's mode of action, has revealed much about its nature and mechanisms of action. When clinical and other studies by the drug company and by many investigators, some supported by NHI research grants, continued to prove the drug effective and safe, it became available during 1962 for physicians to prescribe for their patients.

Cerebrovascular disease

Cerebrovascular disease and strokes are of much interest to the National Heart Institute since the blood vessels are heavily involved in brain disease. Encouraging research developments, illustrated by the following four examples, were reported during the year.

A new method for measuring cerebral circulation has been devised and successfully tested in a glass model and in specially prepared dogs. If the method proves applicable to man, the circulation times in different parts of the brain could be measured and compared.

Initial reports have come in on the use in cerebral angiography of a promising new radiographic contrast agent. Laboratory and preliminary clinical trials have shown that visualization of carotid and vertebral arteries with the contrast medium was excellent and side effects were less than anticipated on the basis of experience with other agents.

Experience with surgical treatment of occluded extracranial arteries located in the neck and upper chest has shown most gratifying results in restoring blood flow and relieving cerebral arterial insufficiency. Of 382 patients with neurological disturbances, 93 percent survived operation. Symptoms were relieved immediately in 85 percent of those with transient cerebral blood insufficiency, in 80 percent of those with progressing strokes, and in 56 percent of those with completed strokes. Followup observations, ranging from 8 months to 8 years after operation, were impressive. Relief of symptoms had been maintained in 90 percent of patients with transient cerebral insufficiency, in 96 percent of those with progressing stroke, and 69 percent of those with completed stroke.

Data continued to be accumulated in the collaborative study of extracranial arterial occlusion in which some 24 investigative teams are currently participating. In this joint study, patients with symptoms of cerebral arterial insufficiency are being studied by angiography and other diagnostic techniques to determine the importance of blocked blood flow in extracranial arteries supplying the brain as a primary cause of the symptoms. Those with occluded arteries judged likely to benefit from surgery are operated upon to remove or bypass the obstruction to blood flow. Data from the participating teams are being pooled in a central registry. Among results from the study may be better criteria for selecting patients for surgery and for determining the optimum form of treatment.

Heart and blood vessel surgery.—Dramatic advances continued in heart and blood vessel surgery along an ever-widening front; in instrumentation; in prostheses—artificial blood vessels, heart valves, patches, and plugs made from synthetic material; in new operative technique; in therapeutic agents and methods use in connection with surgery; and in cardiac physiology and other basic fields.

Uncounted thousands of successful operations were performed upon patients with various kinds of heart disease—congenital defects, rheumatic heart disease, and atherosclerotic damage to the blood vessels, for example. Behind these life-saving and life-extending operations lay step-by-step progress, like that shown in these brief examples of specific research findings of the year, presented in headline form:

Technique Minimizes Hazard of Calcific Emboli After Repair of Aortic Valve.
Whole Body Perfusion Is Simplified by Use of Plasma Extender.
Plastic Adhesive That Bonds Tissue May Prove Useful in Surgery on Heart, Blood Vessels.
Vein Patch-Graft Best for Repairing Blocked Femoral Artery.
Alkalosis Protects the Heart Better Than Acidosis During Profound Hypothermia.
Direct Surgical Approach Used To Repair Aneurysms.
Peripheral Receptors Play Major Role in Cardiac Arrest From Hypoxia.
New Method of Coronary Arteriography Employs Artificial Pacemaker.
Special Catheters Permit Separate X-Ray Studies on Each Coronary Artery.
Researchers Report Many Congenital Heart Operations in 6-Month-Old Infants.

OUTLOOK

Although progress thus far has been gratifying, much remains to be done. It would be pleasant to be able to say that the battle against cardiovascular disease is all but won—that with a major advance here or a breakthrough there, the war will be over. Unfortunately, the mortality statistics presented earlier provide ample evidence that the real fight is only beginning.

In some sectors of the battlefront—congenital heart disease and rheumatic fever, for example—substantial gains have been made. In other sectors, such as atherosclerosis and coronary heart disease, the advances are not as dramatic. However, in these sectors the buildup of basic knowledge is continuing, in the firm conviction that from such knowledge will arise the weapons for future breakthroughs.

There is every reason to believe that breakthroughs can be won and that, ultimately, the virtual conquest of heart disease will be achieved. The evidence of progress of the past year—and the recent years before—bears witness to such a view.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

GENERAL

Research at the National Institute of Allergy and Infectious Diseases embraces human illnesses caused by micro-organisms such as bacteria, rickettsiae, fungus, and viruses, and the widespread allergic diseases, including hay fever, asthma, and food allergy. These afflictions, mild or severe, make up the bulk of day-to-day illness that disrupt the Nation's productivity. The NIAID also studies a variety of diseases of great importance to world health, including malaria, viral encephalitis, cholera, schistosomiasis, rabies, and others.

Approximately three-fourths of the Institute's budget is allocated to support research grants and training at other institutions. The balance is devoted to direct research and administration. The Institute conducts 200 research projects in its laboratories at Bethesda and at its field locations in Montana, Hawaii, Georgia, and the Canal Zone, and supports 2,000 additional studies under the research-grants program. The training programs of the NIAID provide for training grants, postdoctoral and special fellowships (to satisfy generally short-term experience or special training opportunities), research career development awards, and research career awards.

Promising new leads and new opportunities arise constantly. The findings that viruses cause cancers in animals, or that they set the stage for chronic disorders seemingly remote from an infectious process, has provided opportunities for NIAID scientists to collaborate with investigators in other Institutes. Institute scientists have implicated types of adenoviruses (agents usually associated with "colds") in cancer of hamsters. At NIAID's Rocky Mountain Laboratory in Hamilton, Mont., investigations are underway on a virus infection of animals. This virus leads to a degenerative disease called scrapie, which may prove to be a model of viral infection causing certain chronic neurological disorders in humans.

COMMON AND NOT-SO-COMMON INFECTIONS

Mumps, measles, chickenpox, and other infectious diseases usually encountered at one time or another by the average American also are within the purview of the Institute. Its scientists played a part in the first isolations of the German measles virus and in research leading to the development of vaccines against the more common form of measles. Institute grantees are working on an improved vaccine for mumps. In other research, basic studies on chickenpox may define its exact relationship to shingles and to other manifestations of herpes virus infection.

In collaboration with the National Institute of Neurological Diseases and Blindness, a "perinatal project" is under way to determine the contribution of viral infections, during pregnancy, to neurological diseases of children.

VACCINE DEVELOPMENT PROGRAM

The usefulness of vaccine against epidemic influenza has encouraged the development of new vaccines against other infections of the upper respiratory tract—the colds and pneumonias responsible for a billion illnesses each year, with an economic loss of $3 billion The vaccine development program, which began in 1962, focuses on agents that cause a majority of serious respiratory illnesses. These are the respiratory syncytial viruses, parainfluenza viruses, Eaton agent (a pleuropneumonialike organism), adenoviruses, and rhinoviruses. More than 120 different types of viruses of man have been newly recognized in the period since World War II. Many of the virus types under study were first isolated by this Institute's investigators.

Vaccines against respiratory infections can be devised; the problems have to do with virus mutation or change, how pure and safe vaccines can be made, how potent and long-lasting, how rapidly they can be developed, and how many viruses and which kinds can be combined in a single vaccine. Collaborative research with industrial research groups, universities, hospitals, and other facilities is underway. It may take a number of years, however, before vaccines can be made available to the general public.

A number of contracts have been awarded to commercial firms for development of prototype vaccines. Other contracts are being negotiated for clinical evaluation of the new vaccines as they become available for testing.

RESPIRATORY VIRUS STUDIES IN VOLUNTEERS

Clinical studies of viral diseases of the respiratory tract have involved the participation of more than 600 prisoner volunteers from 10 Federal prisons. The men have been inoculated with more than 25 different viruses, including influenza viruses, adenoviruses, and some of the agents that cause pneumonia in young children and are a leading cause of death in the nursery age group.

Work with volunteers enables Institute investigators to obtain much more quickly, and under scientifically controlled conditions, the kind of vital information that could otherwise be expected to emerge only after repeated, long-term studies of naturally infected population groups.

RESEARCH REFERENCE REAGENTS BRANCH

Another activity of research significance under the aegis of this Institute is the Research Reference Reagents Branch. In the growing discipline of virology, there is need of defined biological reagents (antigens and antisera) in the laboratory to aid in the identification of viruses. In the past these materials, supplied by hundreds of individual laboratories, have carried little assurance of comparability. Through its collaborative program, the NIAID is now helping to improve methods of production, storage, and distribution of many important types of viral antigens and antisera.

EATON AGENT-PPLO STUDIES

The "Eaton agent," first discovered in 1944, was recently shown to be an important cause of pneumonia. In collaborative work with the Wistar Institute of Anatomy and Biology in Philadelphia, this agent was grown for the first time in a cell-free medium and was shown to be a member of an obscure group of microbes called "PPLO," or pleuropneumonialike organisms.

ALLERGY-IMMUNOLOGY

Millions of allergic individuals find only partial or temporary relief from hay fever, asthma, allergic skin diseases, allergic headache, drug reactions, and other manifestations of hypersensitivity. Because the precise causes of allergy are not known, much present day research concentrates on fundamental body mechanisms. Allergy-immunology research is conducted in Bethesda, at the Rocky Mountain Laboratory, Montana, and through some 300 grant-supported investigations at numerous medical research facilities throughout the Nation.

Investigations are continuing on a type of thyroiditis suspected of being a disease of autoimmunity, that is, a disease due to an individual's hypersensitivity to substances produced within his own body. Other maladies that may prove to be self-generated include lupus erythematosus, some anemias, certain forms of encephalitis, and a type of nephrosis. Studies of various kinds of therapy in nephrosis patients have indicated that certain drugs called purine antimetabolites (affecting the metabolism of the body) may offer promise in treatment of this and, possibly, other diseases associated with autoimmunity.

Many facets of this problem are being explored through the program of research grants. At the University of Cincinnati College of Medicine scientists conducted immunoelectrophoretic tests of serum specimens from 1,618 infants, most of whom were ill, and were able to correlate precipitins to native milk proteins with certain undifferentiated illnesses. They believe the serum tests provide a rapid means for identifying infants suffering from milk allergy and enabling corrections to be made in their diet.

Other grant-supported investigations deal with methods for removing allergens from the environment; immunological, meterological, botanical, and biochemical aspects of ragweed and hay fever; and the value of desensitizing injections in allergy.

A community study by the University of Michigan School of Public Health is based on responses from 6,995 of about 9,800 residents of the town of Tecumseh, where information on hay fever and asthma cases is being collected, indicates that, although there is frequently correlation between the two, hay fever does not inevitably lead to asthma.

PARASITIC DISEASES

The NIAID is one of the few world centers for research on the essentially parasitic infections—often labeled "tropical disease." Institute scientists have long been sought for advice on world health problems. Instruction in tropical health has been given to U.S. surgical teams sent to tropical countries by the Agency for International Development and to physicians attending Peace Corps volunteers around the world.

Major emphasis has been placed on studies of malaria, the world's No. 1 health problem, afflicting about 200 million people and killing 2 million each year. A hazard to thousands of our nationals in malarious areas, this disease exacts an immense tribute from countries linked economically and politically with our own and it places a hidden tax on a large proportion of our imported goods.

Malaria research is a particularly critical area because of the newly discovered resistance being shown by the common strains of the disease to existing antimalarial drugs. This problem is causing international concern. Certain types of malaria parasites in widely scattered locations are resistant to almost every one of the hitherto effective synthetic drugs.

Recently, the Institute reported trials in prisoner volunteers at the Federal penitentiary in Atlanta, Ga., which demonstrated the remarkable efficacy of a new, long-lasting antimalarial drug (designated CI–501). A single injection of the new drug, developed and supplied by Parke, Davis & Co., afforded scores of volunteers protection from malaria for more than a year. The malaria was induced by heavily infected mosquitoes that were allowed to bite the volunteers at monthly intervals. Other volunteers, to whom to drug was not administered, invariably came down with malaria after being bitten by the same mosquitoes. If the promise of the initial trials in volunteers is borne out under actual field conditions, this new long-lasting drug should greatly aid worldwide efforts in malaria eradication. Evaluation of its effectiveness in malarious regions is now planned in west Pakistan in cooperation with national health agencies.

Research on monkey malaria and its relation to human disease continues in Malaya where the Institute's field group, the Far East research project, is working in an area where a high incidence of malaria occurs regularly. Several new species of simian malaria have been isolated from monkeys and mosquitoes caught in the wild. The Malaya studies have proved that at least one mosquito species, *Anopheles balabacensis introlatus*, is a vector of simian malaria and that this species attacks man as readily as monkeys.

Schistosomiasis, a worldwide parasitic disease spread by fresh-water snails, is also under study by Institute scientists. Paradoxically modern irrigation, impoundment, and drainage systems in some of the undeveloped nations are opening the way for the spread of schistosomiasis, which now afflicts millions in the Middle East, Africa, Asia, and Latin America. This infection might conceivably be controlled if a mass-treatment drug capable of sterilizing adult worms were available, even if it did not produce definitive cure. A pilot study, featuring infrequent administration of low dosages of antimony-cotnaining drugs, has been launched in Egypt to test this thesis. In addition to the collaborative work with Egyptian medical authorities, basic laboratory studies are continuing in Bethesda on the biology and control of snail intermediate hosts of schistosomes.

GERM-FREE ANIMAL RESEARCH

NIAID scientists, using colonies of germ-free guinea pigs, mice, and rats conduct various studies of immunologic and disease processes in the absence of microbial contamination. Data obtained from these fundamental investigations, by indicating any differences between conventional and germ-free individuals, may extend our knowledge of the influences exerted by numerous infective agents on the host animal's physiology. For example, a recent finding demonstrates that intestinal bacteria in female mice enable the animals to ward off certain worm infections which, in males, cause disease. Other females, raised in a germ-free environment, do not exhibit this superior resistance to parasitic infection. Until the introduction of equipment permitting germ-free animal research, scientific information of this kind was unavailable.

MIDDLE AMERICA RESEARCH UNIT (MARU)

Much of the basic work of the Institute in the general field of tropical medicine is performed at the Middle America Research Unit in the Panama Canal Zone. At MARU, which is also supported by the Walter Reed Army Institute of Research, broad programs of investigation are geared toward solution of the residual disorders characteristic of hot, humid climates, especially the rain forests of the Western Hemisphere.

Of special current interest is the so-called Bolivian hemorrhagic fever, a disease that in recent years has caused 200 deaths in northeastern Bolivia and the involuntary migration of hundreds of people from their homes. Other diseases under study are Venezuelan and Eastern equine encephalitis, vesicular stomatitis, histoplasmosis, and leptospirosis.

Together these disorders account for vast numbers of cases of illness and disability, and constitute a major threat to the developing economy of Central and South American nations.

Besides cooperating with the Gorgas Memorial Laboratory in the Republic of Panama, the Institute also maintains close liaison professionally and financially with two major international bodies, the World Health Organization and the Pan American Health Organization. Currently, there are two grants to WHO for the study of virus diseases, viral vaccines, and schistosomiasis. Under the terms of an agreement between PAHO and the Public Health Service, NIAID similarly monitors two additional grants involving the participation of the Pan American Sanitary Bureau and the Institute of Nutrition of Central America and Panama, located in Guatemala.

SUMMARY

The National Institute of Allergy and Infectious Diseases has been impelled to develop extremely broad programs of research for its exploration of the vast world of microorganisms. The basic work in infectious diseases, in fact, supplies much of the technical underpinning for modern medical science, including the investigations carried on by the other institutes in categorial disease areas such as cancer, heart, neurological, and mental disorders.

NIAID research interests range from investigations in the field and clinic to experimental bench research on a variety of disease problems such as allergies, viral infection, fungus diseases, and tropical health problems. Two principal NIAID programs, dealing with vaccine development and production of virus reagents, are aimed at bringing under control those disease agents which are responsible for the majority of respiratory illnesses. Clinical studies in prisoner volunteers are contributing to new understanding of virology, bacterial infections, and parasitic diseases. Future methods of disease treatment and prevention must derive from the insistent probings of today's scientists into the mysteries of the human organism.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Over the years, the National Institute of Arthritis and Metabolic Diseases (NIAMD), originally created for the study of arthritic disorders and disease of metabolism, has expanded its program to include gastroenterological research (digestive tract diseases), endocrine gland diseases, blood and bone disorders, nutrition, and perhaps most importantly, basic research. In terms of potential for future scientific triumphs, many of the NIAMD's most important recent contributions have been in the area of basic research.

THE "CODE OF LIFE"—STUDIES IN BASIC RESEARCH

Since its establishment, the NIAMD has emphasized fundamental research in biochemistry, enzymology, nutrition, and molecular biology. In this last area, molecular biology, particularly exciting developments have occurred, relating to our understanding of the mechanism of inheritance and the means by which inherited traits are expressed.

It has been known for the last decade that the genetic material containing all the information to make a living organism is contained in deoxyribonucleic acid (DNA). This acid consists of sugars, phosphorus, and four different bases, adenine, guanine, cytosine, and thymine, abbreviated A, G, C, and T—but each molecule of DNA may contain 10,000 or more of these bases. It is in the sequence of these bases, whether they are written ACAATG or CATGAA, etc., which tells the cell what to do. In general, what a cell must do in its business of living and growing is to make proteins. About all proteins are composed of 20 amino acids. What differentiates one protein such as myosin, which is involved in muscle work, from insulin, the absence of which causes diabetes, is the sequence of the amino acids. Obviously, there must be some code or language which translates the four letters of the bases into the 20 letters of the amino acids to enable the genes to direct protein synthesis.

It is somewhat more complicated, unfortunately, than a straightforward DNA-to-protein system, because interposed between them is another type of nucleic acid, ribonucleic acid (RNA). This is not too complicated, however, because RNA is also composed of four bases similar to those in DNA. Furthermore, among these four there are pairs with a special chemical attraction for each other. A is always paired with T (or with uridine—U—in the case of RNA) and C is always paired with G. The achievement of NIAMD scientists was in partially deciphering this code. They found that the code seems to run in triplets—UUU means phenylalanine, ACA means aspartic acid, etc. In figure 1 the first three amino acids of insulin are shown as they are probably coded by DNA. The code has been deciphered in many bacteria, viruses, and in mammalian tissues. In all instances it appears to be universal: the lowliest bacteria produces its structure using the same "dictionary" as does mankind.

The exact sequence in which amino acids are joined together is known for quite a few proteins now, so that scientists can begin to learn the exact structure of the chromosome—the very material of life itself.

Other studies in bacterial genetics have ascertained exactly how and in what order the genes for different enzymes are arranged in DNA. On a less ultramicroscopic level, an NIAMD investigator showed that chromosomes of mammalian and other cells can be seen and counted. In fact, in certain diseases abnormalities of the chromosomes can be observed.

These basic studies point up a significant fact. Historically, as medical research has become more sophisticated it has focused on increasingly smaller units of living systems. Today we are at the level of individual molecules within a single cell. We are now beginning to see how these molecules are built from simple starting materials, what shapes they take, and how they organize with other molecules into living systems. This organization might be compared to that of a watch whose many tiny parts must all be present and properly functioning before the watch will tick. We have made some giant strides toward finding out exactly what makes the human watch tick.

PROGRESS AND PLATEAUS IN ARTHRITIS RESEARCH

During the past decade the field of rheumatic disease has experienced a tremendous change as a result of the discovery of the the remarkable anti-inflammatory effects of cortisone. Before cortisone, rheumatic disease was one of the most neglected areas in medicine and little headway was made in either understanding or treating such disorders as rheumatoid arthritis, lupus erythematosus, osteoarthritis, and gout. Cortisone was soon found, however, to be a mixed blessing, for it produced many undesirable, sometimes dangerous, side effects and a continuing search was begun for similar drugs with the same beneficial effect, but fewer or no undesirable side effects. The hope that such drugs might be found or synthesized in the laboratory was partially realized in 1954 when an Institute scientist tested clinically the first effective antirheumatic synthetic corticosteroid drugs, prednisone and prednisolone. These drugs, synthesized by the pharmaceutical industry, were given extensive clinical study at the Institute before release. The search goes on, and, although newer drugs have been introduced, none so far has proven superior in any significant way to prednisone and prednisolone.

Evaluation of new drugs and methods of treatment is a continuing activity of NIAMD arthritis researchers and grantees. In collaboration with scientists from the National Cancer Institute, NIAMD investigators have found that intermittently administered amethopterin (methotrexate)—a drug useful against certain types of cancer—brought about mild to marked improvement in patients with psoriatic arthritis.

In other drug evaluation work, Institute grantees have completed a widespread, multiclinic study of the various types of drug therapy—aspirin, corticosteroids like prednisone, gold compounds, and the newer antimalarial drugs—now used in rheumatoid arthritis. Final statistics are not yet available, but the study indicates that the problems of the multiclinic study technique, which involves close cooperation among a dozen university-connected rheumatic disease centers throughout the country, can be solved and reliable results obtained.

There is no doubt that, although the drugs now used for rheumatoid arthritis are highly potent and irreplaceable for many patients, they are not the final answer to arthritis. Equally important is research into the basic causes of rheumatoid arthritis. During the past 5 years, we have come a long way toward understanding the so-called rheumatoid factors found in the blood of many patients. We know that rheumatoid factors are large antibodies. (Antibodies are special proteins formed in the body, as a defensive reaction to the introduction of foreign substances. They are carried in the blood and are capable of neutralizing the particular foreign substance specifically, when they encounter it.

Antibodies are a part of the body's immunity defense against disease.) It appears that the rheumatoid factors react with a certain fraction (gamma globulin) of the patient's own blood in cases of rheumatoid arthritis, possibly because that fraction has undergone some alteration and has thus become "foreign" to the body. This alteration could be the result of an infectious process.

Another of the continuing studies at the Institute is directed toward families of patients with Sjogren's syndrome, a glandular disorder often accompanied by rheumatoid arthritis. Earlier work had shown that these patients had a high frequency of abnormal antibodies in the blood, and the investigators followed this up to determine whether their relatives also showed this high frequency. They found that these relatives often had a variety of hidden or latent symptoms of Sjogren's syndrome, and indeed had some abnormal antibodies. The closer the hereditary relationship to a patient with Sjogren's disease, the more frequent or severe these manifestations were, indicating that a genetic mechanism operates in the disease.

A unique "population" study of arthritis carried out among the Blackfeet Indians in Montana suggests that the causes of rheumatoid arthritis may differ among racial groups. This work has lent support to the concept that there may be two types of rheumatoid arthritis—acquired and inherited. Several surveys in recent years, both in this country and in Europe, have indicated a genetic cause of both the disease and rheumatoid factors. The Blackfeet study, however, suggested that, at least among the Blackfeet, the disease may be influenced or determined by environment, rather than inheritance.

Gout is another of the rheumatic diseases in which major advances have been made over the past year. This age-old disorder, once considered the result of overindulgence in food and drink, is now understood to be caused by an inherited defect in body chemistry. The defect leads to an accumulation of uric acid in the body, and recurring painful attacks of gouty arthritis.

For hundreds of years physicians have been soothing these painful attacks with colchicine, a drug so specific for gout pains that its effectiveness is considered sufficient for diagnosis of the disease. For centuries the precise action of the drug has been a mystery, since it does not affect uric levels in the blood. Recent work has shown that the drug interferes with the action of white blood cells, which engulf and destroy invading bacteria or other foreign particles in a process known as phagocytosis. In gouty attacks, the objects of phagocytosis are the urate crystals which have formed in body joints. The phagocytizing action begins a vicious cycle of pain, inflammation, and new crystal formation as the white cells engulf the urate crystals. Research has shown that colchicine diminishes the activity of the white cells, breaking the pain-producing cycle of urate crystal formation and inflammatory response.

PROGRESS IN METABOLIC RESEARCH

Intensive study goes into metabolism, an almost boundless research area. Some of the diseases in this area, like diabetes, are quite common, while others, such as alcaptonuria and phenylketonuria, are relatively rare. In view of the fact that "metabolism" is the term given to the sum total of all the chemical reactions taking place in the body, it is easy to see how wide a field the phrase "metabolic research" covers.

Diabetes

Of all the metabolic diseases, diabetes, since it affects millions of people, is probably the best known. From the patient's point of view, the continuing gains made in the treatment of diabetes are among the brightest features of contemporary medicine. As a result of developments like the discovery and widespread use of the new oral antidiabetic drugs, the outlook for persons with diabetes has improved materially in recent years.

The first oral drugs were made available in 1957 by the pharmaceutical industry, and several additional drugs are now in use. The oral drugs have replaced regular insulin injections in more than a third of the Nation's diabetics, and it is now generally accepted that their most important action is to stimulate the beta cells of the pancreas to release insulin into the bloodstream.

One of the most important concepts in diabetes is the emerging idea of "prediabetes," which asserts that impaired carbohydrate metabolism (the standard test for diabetes) is actually one of the later changes to occur in the diabetic, not one of the first. From a genetic standpoint, a person is probably prediabetic at birth, though he may continue to have a normal carbohydrate metabolism for years.

Since it is conceivable that other chemical or perhaps anatomical changes may precede frank abnormal carbohydrate metabolism, investigators have been searching for such changes in the hope that early detection and treatment might prevent the emergence of actual diabetes. One group of investigators has devised several tests, including photography of blood vessels in the eye, and electron microscopy of ear lobe biopsies; early results indicate possible value in detection of the prediabetic. Important steps in early recognition of the disease in currently "normal" obese and in pregnant women stem from related work which has shown (1) that nondiabetic obese subjects may require compensatory, increased amounts of insulin to maintain normal carbohydrate metabolism, and (2) a high incidence of diabetes during pregnancy.

One of the benefits of the oral drug discoveries has been the stimulation of interest in basic problems related to diabetes. One such problem is the abnormal occurrence of amino acids in the urine of many diabetic patients. What relationship this has to diabetes is still unknown, but full disclosure of the mechanisms behind it may bear heavily on the entire diabetes problem. Institute studies, now underway in both diabetic patients and normal volunteers, will ascertain how amino acids are handled by the kidneys, and what role, if any, insulin plays in the kidney's excretory processes.

Histidinemia

In other metabolic studies tiny slivers of insensitive skin clipped painlessly from the fingertips near the nails have allowed NIAMD scientists to pinpoint the basic cause of a newly discovered disease resulting from an inborn error of metabolism—histidinemia. This disease had been first described but 1 year previously, in 1962, by physicians in Canada.

Studies by Institute investigators have now shown that the disease is due to an inherited lack of one of the body's many enzymes. Because of the biochemical similarity between histidinemia and a more serious disorder of body chemistry, phenylketonuria (PKU), the first cases of the new disease were noticed during diagnostic studies for PKU, a disease that causes severe mental retardation if untreated.

None of the histidinemic patients is over 8 years old and the only serious clinical manifestation of histidinemia so far seems to be a speech defect. Study of a larger number of such patients is needed, and consequently a collaborative project has been started by NIAMD scientists with geneticists from the National Institute of Dental Research to screen speech clinics at schools and universities for undetected cases of histidinemia.

Cystic fibrosis

Cystic fibrosis (CF), an untimely fatal disease of children and adults, is thought to be caused by an inborn error of metabolism which produces a widespread disturbance in certain exocrine glands leading to chronic and progressive pulmonary disease and, in a majority of cases, to intestinal malabsorption and malnutrition. Since over 90 percent of the deaths occur because of the lung involvement, trials of newer antibiotics and bronchial mucus-dissolving agents are an important aspect of current research.

In NIAMD's Pediatric Metabolism Branch sensitive screening techniques are being used to locate any abnormal constituents common to all the organs and tissues of cystic fibrosis patients in an attempt to discover the basic defect in CF.

An abnormally high level of salt (sodium chloride) in the sweat of CF patients is a well-known feature of the disease and the object of many NIAMD studies. One involves the detection of individuals who are heterozygotes for the cystic fibrosis gene (persons who carry a partial genetic endowment for the disease) but do not display the clinical symptoms. Recently, a striking difference has been reported between normal subjects and heterozygotes (or hereditary "carriers" of the disease) in their sweat electrolyte responses to stress situations, and work is actively underway at NIAMD to clarify this pattern of response. This may have not only great theoretical importance in helping to identify the defect in the sweat glands, but from a practical standpoint may clear the way for the development of a test for the recognition of heterozygous carriers. This in turn would permit genetic counseling and ultimately reduce the prevalence of this relatively common hereditary disease.

Two other noteworthy accomplishments are the development of a new method for the detection of minute amounts of drugs including narcotics, and the laboratory synthesis of one of the body's major hormones. NIAMD scientists have developed a method that promises to be of value in studying, among other aspects of the use of narcotics, the relapse rate of addicts. This is one of the major areas of research on addiction, and the NIAMD work has provided a rapid and sensitive method for detecting traces of various narcotics in urine samples. This technique, in comparison to older methods which took over 24 hours, can be conveniently used in 4 to 5 hours, and, with modifications, appears to be equally as fast and sensitive for barbiturates, tranquilizers, and antihistamines.

The other study of interest involves ACTH (adrenocorticotropic hormone), the pituitary-produced hormone which stimulates cortisone production in the body. Since the first successful synthesis of ACTH in 1960 by Institute grantees at the University of Pittsburgh (one of the important biochemical accomplishments of the past decade), the researchers have continued to move ahead. Confident their techniques would be useful in producing tailormade hormones with the specific desirable characteristics of ACTH but free of any unwanted effects, they have synthesized a number of ACTH-like peptides displaying a variety of significant biological actions.

GASTROENTEROLOGY—TEN YEARS OF CHANGE

Gastroenterological research, encompassing all the diseases of the digestive tract, is in a state of dynamic transition. A significant factor has been the granting of increased funds for research by the Institute. This support has been effectively used.

One of the developments, illustrating the fruitful cross-fertilization taking place between physical scientists and medical scientists, was the invention of a new diagnostic tool for examining the gastrointestinal tract.

This endoscope employs flexible optical fibers for its viewing elements and so bends to follow the curves of the digestive tract. It makes possible direct examination of many areas previously inaccessible to the conventional rigid gastroscope. The inventor of this tool is now using it for much-needed direct studies of the gastrointestinal tract.

Much attention has been focused on the biochemical aspects of the digestive process, and recent work on Whipple's disease is a prime example of progress in this area. Whipple's disease is a grave metabolic disorder marked by loss of weight and strength related to a defect in fat absorption by the intestine.

Patients with Whipple's disease in relapse characteristically exhibit abnormally low concentrations of albumin in their blood. In order to determine the cause of the low blood albumin, tests were carried out by NIAMD scientists, working in collaboration with scientists at NCI, and it was shown that the patients were "leaking" abnormally large quantities of albumin from the blood into the gastrointestinal tract. Using a form of therapy first introduced by an NIAMD grantee, namely, the administration of corticosteroids and antibiotics, the NIAMD group found that the albumin leak could be reversed with striking rapidity, even before the structural changes in the intestine improved, and thus would permit a return of the blood albumin levels to normal.

This study points up some of the unique characteristics of the Institute's clinical program: Whipple's disease is so rare that a single institution may never see one case, yet NIAMD scientists were able to study six intensively. This rare disease is important because it may yield clues to the general problem of intestinal malabsorption, a condition present in numerous other gastrointestinal disorders.

KIDNEY DISEASE

Recently, Institute grantees developed a new, practical, and effective technique which, through the use of permanently implanted plastic valves, permits the repeated "hooking" up of patients who have lost their kidney function, to artificial kidney machines. These machines remove from the blood harmful body wastes (ordinarily removed by healthy, functioning kidneys), which would otherwise accumulate and would ultimately lead to death through uremia. During the past 2 years, a number of patients have benefited from this lifesaving method of treatment, given twice weekly, and it has considerable potential for future care of patients with serious kidney disease.

INTERNATIONAL NUTRITION RESEARCH

In addition to its own nutrition research, the Institute supports the research activities of the Interdepartmental Committee on Nutrition for National Defense (ICNND). During the past 2 years the Committee's research work has been largely epidemiologic—determining the incidence, distribution, and interrelationships of nutritional diseases in different populations and different geographic, climatic, and economic environments. The studies have yielded a variety of new information of considerable importance to the United States. A study in South Vietnam, for instance, of goiter has resulted in the development of a new index of dietary iodine intake.

Other studies in this area have uncovered some evidence for a hitherto unsuspected role of vitamin E in the formation of red blood cells. This type of research is not only relevant to domestic health problems and health needs, but points out new directions for biomedical research.

OTHER RESEARCH SUPPORT

A major key to succesful research to better our Nation's health is the development of highly trained, skilled, and imaginative scientific manpower. For this reason the Institute continues to emphasize the need for support of research training and continually seeks ways to develop new and more effective research training programs.

NIAMD uses training grants and postdoctoral fellowships to train young physicians and scientists. It seeks more effective ways to train young men and women for clinical research careers. This Institute's experimental program of training for clinical investigators seeks to revise and strengthen training methods at selected institutions and make them more responsive to medical research needs. Specifically, it seeks to condense the training period between the third year of medical school and the third to sixth year after medical school graduation. It seeks, also, to impregnate the residency system with training experience in high-quality laboratory research techniques and understanding of sophisticated research methods.

A new experimental NIAMD program is designed to develop more effective ways of training young men and women for careers in clinical research. The experimental program of training for clinical investigation will enable a selected number of institutions to strengthen and make extensive revisions in their training methods for clinical investigators with an eye to the future manpower needs of medical research.

The Institute has long carried on a program of sicentific communications including the stimulation and promotion of interchange between scientists through conferences and meetings, support of special scientific publications, and preparation of scientific exhibits and pertinent literature on the latest advances in specific diseases, which are brought to the attention of thousands of practicing physicians. Recently the NIAMD has provided a grant for research on the establishment of a comprehensive diabetes information retrieval system, combining facilities for collecting, abstracting, and translating all scientific diabetes data published anywhere.

NATIONAL INSTITUTE OF DENTAL RESEARCH

RESEARCH—ORAL DISEASE

Problems of oral health and disease are widespread in our country. They affect the lives of all of us. Pain, expense, and disability connected with diseases of the teeth and their supporting structures provide impetus to the research which seeks the causes, the treatment, and ultimately the means of prevention of oral disease.

The most important causes of disability are dental decay, periodontal diseases, abnormalities of growth and development (such as cleft lip and palate), oral ulcerations, and oral cancer. Since 95 percent of the population suffers from dental caries (tooth decay) and practically everyone over middle age has some form of periodontal disease, the importance of research is obvious. The 6,000 children born each year with cleft lip and palate and the existence of other congenital deformities of the mouth and face constitute another urgent reason for research. Similarly, the growing knowledge of cancer needs to be extended to the study of the malignancies of the oral and facial area.

Successful resolution of these problems is dependent upon research, and research is dependent upon the availability of trained scientists who can find out the new and communicate it, not only to their fellow scientists, but to the dental practitioners and the American people.

One-fifth of the Institute's budget is used to carry out research in its laboratories in Bethesda, and four-fifths to underwrite research and training in more than 125 universities and research institutions throughout the country. All 49 schools of dentistry and some hospitals participate, through grants, in research and educating the research scientists of the future.

Dental caries

Recent research has shown that tooth decay in animals is a disease of bacterial origin. Animals grown in germ-free tanks, where bacteria do not touch them, do not have decayed teeth. Scientists have identified a specific strain of streptococcus which causes tooth decay in hamsters, and another specific strain which causes similar decay in rats. The scientists have not only found the organisms which produce decay, but have succeeded in transmitting the disease from one animal to another.

Today these laboratory leads are being carried into clinical investigations through study of comparable situations in human beings. Groups of children are being studied to see whether the elimination or diminution of certain bacteria in the mouth can cut down or eliminate decay of the teeth.

Although dental decay may be caused by specific bacterial agents, it is related to a complex interaction of several factors, including diet and the protective mechanism which the affected subject may have inherited. Thus, if the protective mechanism is adequate, there is no decay; if the diet is not the right kind to support a flourishing growth of the causative bacteria, there is no decay; and if there are no bacteria of the decay-producing variety, there is no decay.

Research has concentrated on all aspects of this disease cycle. For example, work is proceeding on how bacteria can be eliminated, and the influence of dietary factors such as the quantity and quality of protein, carbohydrate, and various chemical compounds, particularly of organic and inorganic phosphates. Among the more interesting results are that carbohydrates (starches and sugars) are decay-stimulating foods, while phosphates added to the diet of caries-active laboratory animals tend to inhibit the decay process. Also, laboratory animals which nibble food all day have more tooth decay than those which eat only at established meal intervals.

The high degree of protection against tooth decay by means of water flouridation has been fully documented both by research and by wide experience, and today over 50 million Americans are utilizing this public health benefit. This advance had its beginning when Dr. H. Trendley Dean, the first Director of the National Institute of Dental Research, started an investigation in the early 1930's of a curious mottling of the teeth seen in certain geographic areas. This mottling turned out to be due to an excess of fluoride found naturally in the local water used for drinking and cooking. However, when the chemical element was present in very small amounts (one part of fluoride in a million parts of water) it would protect the teeth against decay without any accompanying discoloration.

Final field examinations were made this year in one of the communities that has fluoridated its water for 17 years. Tooth decay in children who had had this water since birth was found to be one-third as severe as in other cities which did not have fluoridation. These beneficial effects have been shown to carry into adult life.

Because there are areas where fluoridation of water is not practical, research is going on to find other means of providing fluoride, perhaps by incorporation in toothpaste, salt, food, or pills.

Periodontal disease

An even more difficult problem than tooth decay is periodontal disease, commonly called pyorrhea. This destructive process involving the gums and structures supporting the teeth causes loss of perfectly sound teeth.

Preservation of teeth through fluoridation, diet, and better care is nullified by the attack in middle age of periodontal diseases. By the age of 50, nearly half our people have lost some teeth through disease of the gums and supporting structures; by the age of 65, almost all people have suffered from this condition to some extent.

The causes of peridontal disease are not known. Research shows that various species of streptococci outnumber other bacteria in the formation of calculus (tartar), which is perhaps the most important immediate provocant of periodontal disease. However, the bacterial factor is not the only one, since other research this year has shown that tartar formation can occur also in animals brought up in germ-free tanks where bacteria do not exist. Parallel studies have indicated that a virus isolated from rats can produce severe periodontal disease in hamsters; and more recent laboratory studies have led to the isolation and identification of a specific filamentous bacterium capable of producing a type of periodontal disease in hamsters similar to chronic periodontitis in man.

Research at this stage points in several directions. Scientists are now trying to learn just how and why tartar forms on the teeth, what can be done to prevent its formation, and what effect it has on the later periodontal disease state.

Since micro-organisms, whether viral or bacterial, are linked with certain kinds of peridontal disease, the eventual prospect for some degree of control is encouraging. There is, however, the continued problem presented by the likelihood that periodontal disease may in fact be several different diseases rather than a single, defined entity.

Mouth and face abnormalities

Major research is being mounted today to eludicate the factors which produce cleft lip and palate, among the most common of congenital deformities. Multidisciplinary research centers have been established through grants from the Dental Institute at six different universities or institutions to study this problem in its many aspects. Causes are being sought, as well as better methods of surgical treatment, speech rehabilitation, prosthetic repair, and social and psychological adjustment.

One new instrument measures and graphs airflow from nose and mouth during speech and so makes possible a study of the fine articulations of speech; another device permits better nourishment of babies with cleft palate during the time before they can be operated on. New techniques have been used to study the genetics of hearing loss; the identification of areas of sensation of the mouth and pharynx by which respiration is modified; and the motions of the oral and pharyngeal structures during the course of speech. These studies, now in progress, provide data which aid the surgeon to repair palatal clefts at the most favorable time and in the most effective way.

While this research helps the patient with cleft palate to become a more "normal" individual, to speak more normally and to live more normally, genetic studies now underway may help us to understand how some clefts occur in the first place. Such studies have included a description of chromosomal abnormalities in patients with oral and facial deformities, and a determination of familial patterns of abnormality in isolated populations with large numbers of cousin marriages. The study of relationships of genetic factors, not only to cleft lip and palate, but to defective calcification, susceptibility to dental decay and other oral diseases, is a difficult and time-consuming task. Nevertheless, scientists have recently been able to trace definite genetic evidence for the transmission of certain diseases of defective enamel and dentin formation, defective speech, and a syndrome of mucosal changes affecting the mouth and eyes.

Oral ulcerations

Aphthous stomatitis (canker sores) is a troublesome and recurring mouth ulceration for which there is no known specific cause and no known specific treatment. Research now points to an unusual micro-organism as a possible cause. This so-called transitional L-form of bacterium is like its bacterial parent but represents a different phase. With an adequate stimulus, such as trauma, the cyclic transformation of the germ from one phase to another, with several intermediate stages, may occur and thereby initiate a recurrence of ulceration.

The familiar herpes simplex or fever blister is another mouth ulceration being studied by dental research scientists. This condition is caused by a virus, but the investigators now have discovered that even in the same individual the recurrent attacks of such herpes infections may not be caused by the same strain of virus. This observation throws a new light on the natural history of this common infection, which usually has been attributed to exacerbations of the identical virus.

Oral cancer

One in twenty cancers occurs in the oral cavity, whether in lips, cheeks, floor of the mouth, tongue, palate, or gums. Extensive research is going on to determine the possible cancerous effect of local irritants on the oral tissues. In other programs, exfoliative cytologic methods and fluorescent microscopy are being used in the diagnosis of oral cancer. Paralleling these activities are studies to better understand leukoplakia, a condition which may predispose to the development of cancer.

RESEARCH, BASIC

Underlying the research in the various dental diseases is the basic scientific work which leads to an understanding of disease processes themselves. Every advance, whether in diagnosis or treatment, is based on years of fundamental studies in basic biological sciences. Many disciplines are included and all are important.

Microbiology has developed new knowledge of the role of bacteria and viruses in dental diseases. Most broadly significant perhaps is the emerging concept of microbial specificity; i.e. specific micro-organisms accounting for particular oral pathologic conditions. Coordinated major attention also is being given to the complex and varied phases of host-parasite interactions influenced by our peculiar environments.

The pathologists have developed an accurate system of age determination by microscopic examination of teeth, something of importance not only to the field of legal medicine, but also to the anthropologists who study the development of man from paleontologic times.

Chemistry and physics have given science new techniques for determining chemical elements in dental tissues by the use of monochromatic X-rays for microradiology, and are now leading the way to the development of materials which will have greater adhesive properties for the restoration and repair of teeth.

Genetics, crystallography, protein chemistry, enzyme chemistry, electron microscopy, nutrition, epidemiology are among the biomedical and physical sciences which today share in this expanding world of dental research.

A particularly important observation has been made by the crystallographers. Human bones with relatively high fluoride content tend to have more perfect crystal structure, thereby increasing their physical and chemical stability. These findings are related to the fluoride effect on teeth. Bones and teeth are similar in makeup, and the fluoride which strengthens the crystal structure of bone probably does the same for teeth. We have known for some time that fluoride works. Now, for the first time, we have some evidence as to how it works.

The field of biomathematics is also important in dental research. Large population studies in many parts of the world are being analyzed by computer methods, so that many factors—climate, nutrition, family background, social practices—can be simultaneously evaluated.

The histochemists have developed new staining techniques to demonstrate a connective tissue fiber characteristically observed in areas of stress. This will help in the study of connective tissue disorders.

Each step in dental research, each gain in understanding of disease conditions in the mouth and teeth, is based upon the basic and fundamental research of the scientist in the laboratory. The knowledge which builds tomorrow's healthy population is bred in the studies of the biochemist, the microbiologist, the histopathologist, the crystallographer, and all the other basic scientists. Studies which seem so far removed from disease at the start produce results which ultimately create future cures.

Study of the mineral structure of the snail shell, for example, can lead to an understanding of biological mineral of all kinds, thence to an understanding of teeth and bones, thence to diagnosis, treatment, and prevention of disease states in these structures of man. The health of the future lies in the research laboratories.

TRAINING

Of great importance to the future of dental research are the graduate research training programs under Dental Institute sponsorship in basic and clinical sciences related to the various dental specialties in many dental schools and universities throughout the country. The training support made available to these institutions represents the major source of funds available to develop much of our manpower for dental research in the decades ahead.

Of interest also are these developments: (1) A program to train clinical research scientists by encouraging highly qualified students to acquire both the Ph. D. and eligibility for Board certification in a dental specialty, and (2) training programs in university departments which have specialized competencies of importance to dental research, but not associated with dental schools per se.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

The National Institute of General Medical Sciences administers the NIH grant programs for research and training in the sciences basic to medicine and biology, to public health, and to certain clinical sciences and research not covered by other institutes or divisions. In addition, the Institute provides fellowships for general research training. Knowledge gained from them nourishes all of the life sciences and serves to undergird the other NIH research programs, which are primarily disease oriented.

RESEARCH GRANT ACTIVITIES

The research coverage of the Institute is broad. Included in its programs are the natural and behavioral sciences, such as anatomy, biochemistry, biomathematics, biophysics, molecular biology, cellular biology, enzymology, epidemiology, genetics, microbiology, pharmacology, cultural and comparative anthropology, and sociology. Certain clinical sciences are also included, such as general surgery, diagnostic radiology, pathology, and anesthesiology, as well as various methods of science, including electron-microscopy and biostatistics.

An indication of the depth and breadth of the program is illustrated by a breakdown of one segment, the biomedical research supported by the Institute, which is grouped under the following broad categories:

Basic Biological Sciences, including various phases of cell biology, genetics, embryology and development, physiology, metabolism, nutrition, radiobiology, and microbiology.

Chemistry of Life Processes, including biochemistry, biophysical chemistry, biophysics, physiological chemistry, medicinal chemistry, pharmacology and toxicology.

Methods and Tools of Science, including both the development of coding technics and the application of computer methods to the solution of biological problems ranging from the analysis of electrocardiograms to the determination of molecular structure by the analysis of X-ray crystallographic studies, development of a sensitive, high-speed cell scanner and counter, new technics for the analysis of various kinds of data and processes.

Clinical Sciences, including studies in anesthesiology, endocrinology, pathology, and general surgery.

In one research area of special emphasis in this category, answers to questions about the physiological reactions to anesthesia are being sought. Fundamental research into the molecular reactions by which so-called inert gases can produce the profound physiological changes associated with unconsciousness is now underway, but it will be sometime before the significance of such studies is established.

There is need to know much more about the physiological reactions of different age groups with different disease conditions to specific anesthetics. The widening of the margin of safety and the reduction of deaths from anesthetics will depend upon future research on equipment, methods, and physiology. The reduction of anxiety and fear, and the psychological and behavioral aspects related to anesthesia need to be studied.

Not too long ago, it was considered that the range of investigational interest in the life sciences extended only down to the cellular or subcellular level. Today, it is recognized that biology must concern itself not only with molecular relationships, but also with submolecular phenomena. It is becoming apparent that each part of a molecule of protein or of a nucleic acid has a special significance in terms of specific activity and function. Scientists today are concerned with new dimensions in the study of submolecular structure and of the relationships of chemical processes to health and disease. A beginning has been made in the recognition of specific molecular diseases such as cystic fibrosis, galactosemia, histidinemia, and Wilson's disease.

Underlying the approach to such complex and poorly understood diseases is basic research in genetics. It is here that investigators seek an understanding of the total metabolic process and how it relates to the ultimate control of many disorders of development and of other life processes. For the highly trained scientists who are charting the biochemistry and biophysics of genetics, this field is the most challenging frontier in the biological sciences.

NIGMS-supported research discoveries have been unusually noteworthy, and have led to new knowledge of metabolic disease, allergy, immunity, inflammatory disease, arthritis, and other diseases. Notable has been the isolation and identification, by one investigator of the adrenocorticotrophic hormone (ACTH) and five other hormones of the anterior pituitary gland. He also synthesized a smaller molecule, containing about one-half the natural hormone's amino acids and having approximately half as much activity in stimulating the adrenal gland. He later synthesized a smaller fraction, which shows only slight adrenal-stimulating activity but promotes the breakdown of certain types of fats in the body.

One researcher, whose work has had NIH support since 1948, recently announced some significant discoveries concerning the thymus gland. After 10 years of work, he and his associates succeeded in isolating two powerful chemical substances from the thymus gland of calves: a potent promoter of growth, and an equally potent growth inhibitor. These properties were exhibited also in experimental cancer in mice. More recent studies by the same investigators suggest that the growth-stimulating factor, "promine," actually consists of two substances, a growth-promoter, and a juvenility or sterilizing fraction. These investigations have broad implications.

At Harvard University an NIGMS grantee, in association with a British scientist, has elucidated the helical structure of deoxyribonucleic acid (DNA). This molecule holds the key to the "genetic code," which furnishes instructions for the production of proteins and genetic material. The study of heredity, cancer, viral disease, mental disease, and a host of disorders designated as "inborn errors of metabolism" will be advanced by this fundamental achievement.

A great deal of support has gone to research in genetics, especially the structure and function of RNA and DNA, an area strongly supported by the NIH. While much is known about the structure and energies involved in the activities of DNA and RNA, much more needs to be learned before it can be said that the genetic code has been solved.

Bit by bit, evidence is being uncovered as to the manner in which DNA, RNA and proteins perform their functions, and on regulatory mechanisms that operate in the unfolding of their activities. With each forward step in knowledge from basic research in these areas, new insights are gained in the fundamental life processes as they determine health and disease. Progress will come as a result of contributions from scientists representing many disciplines in the biological and physical sciences, because it is the nature of all sciences to have a convergent interest: the enhancement of human well-being.

In a direct sense, the research activities supported by the National Institute of General Medical Sciences, which are concerned with the understanding both of normal biology and of disease processes, furnish reserves of knowledge fundamental to the programs of other institutes which support the applied or categorical sciences and, in particular, the clinical sciences.

RESEARCH TRAINING ACTIVITIES

The training programs of the National Institute of General Medical Sciences have as their central mission the development of training opportunities and the support of research training in the fundamental health sciences. Like the Institute's research grants program, this activity serves as a base for disease-oriented programs, and thus is an indispensable source of strength to all of the Institutes at NIH.

The graduate research training program is dominantly predoctoral and disciplinary in its orientation. Support is given in 20 or more areas: Anatomical sciences, behavioral sciences, biochemistry, biomedical engineering, biometry, biophysical sciences, clinical research (anesthesiology, radiology, and surgery), computer research, epidemiology, genetics, microbiology, multidisciplinary biological and medical sciences, nutrition, pathology, pharmacology, physiology, and toxicology. Each of these programs functions under the guidance of a training committee or ad hoc group of non-Federal scientists in the particular field in question. These programs support areas of recognized importance to basic biological research and research training. Disciplines receiving support, already listed, give broad coverage to the basic biomedical disciplines which are the foundation of research in health and disease.

Many of these graduate areas represent critical research manpower needs and are being given special program emphasis. As an example, research in the basic behavioral sciences is a matter of growing importance and, indeed, urgency. Training in this area will supplement the programs of the National Institute of Mental Health. The initial goal has been the establishment of training programs is social anthropology, and in the basic elements of the learning process.

Another field that is demanding development as a key interdisciplinary area is biomedical engineering, which is concerned with the development and application of measurement and control systems in connection with biological investigations and medical procedures. While it has been inevitable that biology and medicine should form a partnership with engineering, there have been practical difficulties in achieving this welding of interest in the training of individuals. In the years ahead, biologists, physicists, chemists, engineers, and mathematicians will be expected to take advantage of the increasing availability of new instrumentation.

Clinical pharmacology and toxicology are new disciplines in the graduate complex for which specific training has not yet been generally developed, yet for which the manpower needs in research are extremely critical. NIGMS is attempting to help plan and support training in these areas. Centers for research and training are to be developed by the joint support of both training grants and research grants which bring together both preclinical and clinical sciences. Several years will be required for the realization of this new program.

A new program, the medical scientist training program, is now under development, and is aimed primarily at the provision of research physicians who have received a graduate level of training in both the basic and clinical sciences. Carefully selected candidates will be prepared for research and academic careers in medicine through a pre- and post-M.D. program designed specifically for the purpose. Only those medical schools associated with sufficiently strong graduate school departments would be supported through this program.

A second new program, allied to the medical scientist, is the clinical research training program, which gives post-M.D. training. Its purpose is to provide fundamental science training to clinicians desiring to pursue research careers in such fields as anesthesiology, radiology, or surgery.

The research training programs of NIGMS try to anticipate the Nation's future needs for graduate research manpower in the academic and governmental environments concerned with the health and the health-related basic sciences.

FELLOWSHIPS

Supplementing the training grants activities are three levels of fellowships—predoctoral, postdoctoral, and special fellowships—which support the training of competent scholars in health and health-related sciences by direct award to individuals. Emphasis is placed on the basic biomedical sciences, with support also given to some of the behavioral sciences. The awards, made to individual predoctoral and postdoctoral candidates plus those who wish training in special areas, provide specific support for training in conventional disciplines as well as in new research fields and in interdisciplinary areas.

In addition, the research career program is available to provide stable career opportunities for qualified candidates of superior potential and capability in the health-related sciences. Under this program, development awards are designed for young investigators who need further experience to qualify for senior positions. On the other hand, career awards are for experienced investigators pursuing careers of independent research and teaching. These are awarded with the intention of continuing Federal support for an individual's entire career.

PROGRAM ANALYSIS

With the growth of the Institute's programs, it has become necessary to provide adequate machinery by means of which proposed and existing activities may be evaluated at many levels. To implement this, the Institute has established a Program Analysis Branch which is charged with the responsibility for providing a variety of materials to form the basis for program evaluation and planning. Our prospects for adding to the Nation's storehouse of knowledge in the basic medical sciences will be enhanced materially by a resource for data accumulation and retrieval which will become available through this source.

NATIONAL INSTITUTE OF MENTAL HEALTH

MENTAL HEALTH TRENDS

The National Institute of Mental Health from the time it began functioning in 1949 as the Federal agency concerned with control of the mental disorders, has focused on research aimed at prevention, treatment, and rehabilitation of the mentally ill, and on training to increase the number of qualified mental health personnel. It has also provided funds to stimulate State and local mental health services.

Federal support of State mental health activities has been on a matching basis. In 1962, for example, some $6 million of Federal support was matched by a total of approximately $85 million budgeted by State and local governments. The Federal share has decreased proportionately over the years, as State contributions have mounted, with Federal support serving as a "seeding" to stimulate increased local activities.

Dramatic evidence of the success of mental health activities has been the steady decline in the number of patients in mental hospitals. As a result of new approaches and methods of treatment developed during the past decade, including the use of psychoactive drugs, hospital populations have declined every year for the past 7 years, with the largest drop noted last year. This has occurred in spite of rising admissions, increasing in number almost 50 percent since 1955. Net releases show an even greater (75 percent) acceleration. Data from the NIMH indicate that the 515,948 patients resident in public mental hospitals at the end of fiscal year 1962 represent a decrease of more than 2 percent from the corresponding numbers at the end of 1961.

The trend is particularly significant in view of the high price society pays for mental illness. More than $2.4 billion in public funds are expended each year for maintenance of the mentally ill and retarded. Had the number of resident mental patients increased along lines projected in 1953, before the discovery of the psychoactive drugs and refinements in therapy, there would have been almost 20 percent more patients in hospitals today.

The NIMH has played an important part in stimulating research and related activities that have brought this about. By supporting many demonstration projects and studies that have provided steadily accumulating evidence of the effectiveness of community-centered facilities as opposed to long-term custodial care in mental hospitals, it has made possible a major breakthrough in treating mental illness. It is now apparent that most mental patients can be successfully treated with short-term intensive therapy in community mental health facilities, and do not require long-term custodial care. Accordingly, a major aspect of the Institute program will be increasing efforts to stimulate community mental health facilities, ranging from preventive measures through intensive treatment, aftercare, and rehabilitation programs.

In February 1963, President John F. Kennedy, in a special message to Congress, called for a nationwide program of comprehensive mental health centers for communities as an essential step toward control of the mental disorders. New legislation, calling for substantially increased Federal support for planning and construction of community mental health centers, was enacted by the 88th Congress in 1963.

As this program is implemented by States and localities, it is expected that the traditional State mental hospitals known today will change, taking their place as one part of a continuum of services, including emergency psychiatric services, short-term intensive treatment, day and night hospitals, aftercare programs, vocational rehabilitation, nursing and foster home care, and intensive treatment for the chronically ill.

The rationale for such a revolution in the care of the mentally ill has been stated by Dr. Robert H. Felix, Director of the NIMH:

"In view of what has been learned in recent years, it is evident that the large mental hospital is not the most desirable place for most sick minds. There is no valid reason why mental illness to a great extent cannot be treated in the same way as any other illness—in a doctor's office or local hospital if necessary. When a person needs help is not the time to wrench him from family and friends, all that is familiar, and deliver him to a strange institution. What the mental patient needs as much as drugs and professional treatment is a good therapeutic environment. And since the patient must go back to his own community when he is healed, it is best for him to be treated there. The principal objective of the new trend in mental health programs is to make seeking help as simple and uncomplicated as getting medical attention for a physical illness."

TRAINING

Obviously, with more than 1 million persons requiring some sort of treatment for emotional disorders each year, the need for competent trained personnel is acute. Much of the emphasis of the NIMH program has therefore gone toward support of such training, as well as training for research.

Training and fellowship programs of the NIMH have supported training of the core mental health professions—psychiatrists, psychologists, psychiatric social workers, psychiatric nurses. They have also supported research training in the biological and social sciences; mental health training in schools of public health; orientation for lawyers, educators, and clergymen among others in special areas; orientation of general practitioners to play a more effective role in psychiatric treatment; programs in medical schools to enable physicians to utilize mental health concepts.

From 1948 through 1961, approximately 12,000 persons received graduate training stipends. Twenty-five hundred fellowships were also awarded for research training at the graduate and postgraduate levels. Additional thousands received training in mental health concepts and skills in undergraduate programs in psychiatry and psychiatric nursing, in training programs for general practitioners, and others. The Institute is now looking forward toward another training development—provision of inservice opportunities to upgrade workers in service settings, such as administrators, occupational therapists, aides, and other personnel.

RESEARCH

Despite tremendous advances along many research fronts in recent years, the cause of major mental illness still remains to be found. The complexity of the problem of mental illness, involving mechanisms that underlie behavior, and involving the brain and the nervous system as well as psychological and social and environmental stress, requires that many diverse disciplines come together in a broad attack.

Nowhere is this broad attack better illustrated than in the area of schizophrenia, where research encompasses medical, biological, psychological, and social sciences. Clues to prevention, cause, and treatment are being sought in the chemistry of the body as well as in the quality of the mother-child relationship; in the mechanism of the brain along with the social structure of the community; in the effect of psychoactive drugs and the dynamics of the patient-therapist relationship. The contributions of the biochemist merge with those of the psychopharmacologist; the findings of the anthropologist with those of the social psychologist; and often members of highly divergent disciplines work together as members of a single research team.

It has now become apparent that the cause of mental disorders may reside in genetic factors, metabolic errors, psychological stresses, and social experience, and that two or more of these factors may be involved in any clinical problem. The Institute is therefore supporting research along all these fronts.

Much of the research program falls within the area of behavioral sciences. The specific relevance of these sciences to mental health problems is underscored by the fact that the phenomena of the mental disorders make themselves known primarily through behavior.

Such research serves to clarify the role of psychological and social factors known to be important in the etiology, prevention, and treatment of mental and emotional disorders; it advances attempts to identify additional variables related to mental illness, and to improve techniques for measuring them.

Studies of a more basic sort, in which investigators seek to increase the fund of knowledge about basic social and behavioral processes themselves, are also essential to the mental health research program.

As an example of the diversity of mental health research, last year more than 30 professional disciplines were represented among the scientists receiving grants, and more than 20 different types of academic departments were associated with those projects sponsored by colleges and universities. Among major areas of health and social problems being investigated, besides schizophrenia, were mental retardation, juvenile delinquency, alcoholism, drug addiction, aging, psychopharmacology, and child personality and development. In the pursuit of biological and biochemical factors related to mental illness, neurobiologists, neuropharmacologists, biochemists, physiologists, and microbiologists, and biophysicists are pushing forward on many fronts, and many new and promising clues have been revealed.

It is generally recognized that the orderly system of chemical reactions through which metabolism of body substances takes place is genetically determined. Because certain behavior patterns appear to be associated with the nature of chemical reactions in the metabolic process, the Institute supports an increasing number of studies seeking to identify the relationships among genetic aberrations, metabolic processes, and adaptive behavior. In some studies, scientists are investigating the metabolism of serotonin, acetylcholine, steroids, catecholamines, and other substances believed to be involved in mental and emotional processes. In others they seek some unidentified toxic agent in the blood or urine of schizophrenics—a substance which many feel is at least partly responsible for the development of this disorder. Several laboratories have reported the discovery of substances which, when injected into laboratory animals, bring about behavior changes which resemble in some aspects the disturbed behavior of the mentally ill. While the discovery of such a substance holds enticing promise of a dramatic breakthrough, considerable difficulty has been encountered in isolating or identifying the substance or substances inducing these effects. The complexities of the biochemical processes, coupled with the complexities of human behavior, suggest little likelihood of discovery of a simple one-to-one relationship between some aberrant metabolite and mental illness. Some scientists believe that the phenomenon causing dysfunction may in fact occur at a submolecular level; all concede that much preliminary basic research must be done before the enigma of mental disease is unraveled.

The findings from various scientific laboratories providing evidence of some biochemical or metabolic abnormality in mental illness indicate the need for further pursuit of this significant lead.

Investigation of the biological basis of mind and behavior involves study of the myriad physical and chemical structures and interactions which form the essence of the complex functions of the brain. New instrumentation and techniques have vastly extended research in this area. Studies have been made possible, for example, of the electrical charges and discharges of single cells.

One investigator has designed and built a functional system for cortical recording from many closely spaced electrodes, the net effect of which is to provide a motion picture of the electrical activity in an animal's brain. This device has opened up new possibilities for the study and analysis of sensory, motor, and learning phenomena at a hitherto impossible level of sophistication.

Another investigator has developed a technique whereby the retina of a rabbit and its attached nerve can be isolated and kept in a functional state in vitro. In a sense this preparation can be considered a partial model of the nervous structure of the brain itself. With the use of newly developed micronanalytical techniques, this scientist is conducting studies of electrolyte metabolism, synaptic transmission and related electrophysiologic phenomena. Adaptation or modification of this technique should enable other researchers to undertake neurophysiological studies never before possible.

Considerable work is being conducted on the neural mechanism of reinforcement, based on earlier findings demonstrating the existence of specific areas of the brain controlling emotional responses. Some scientists are searching for specific areas governing reward and motivation, as these relate to the satisfaction of primary drives such as thirst and hunger. Others have offered evidence to show that primary drives are mediated by circuits in the brain rather than the response of single or isolated loci. While the existence of a series of structures of the brain composing an interconnected functional circuit related to the expression of emotion had been previously postulated, experimental evidence was not obtainable until the recent development of brain-stimulation technique and the use of biochemical methods utilizing the selective sensitivity of specific portions of the brain to a variety of newly discovered chemical agents.

Familial factors

In the area of psychological and psychodynamic studies of mental illness, certain NIMH studies indicate that in families in which one member is schizophrenic, there are peculiar patterns of thinking which are relevant to the patient's condition. In one recent study of protocols from testing sessions, a projective test expert, knowing none of the subjects of the study, was able to identify the members of individual families through common ways of thinking. She was able to allocate 16 of 18 patients correctly to the family in which the patient belonged. This is done not on the content of thinking involved in the test answers, but of the form of thinking. The implications of such research are of striking importance in understanding the psychological context in which schizophrenia develops.

Psychopharmacology

The Institute conducts a vigorous program in psychopharmacology. The integrated program of research now underway includes a series of collaborative clinical studies designed to assess the efficacy, specificity, and safety of known drugs reported to be useful in mental disorders. A group of investigators are also carefully evaluating new chemical agents to determine whether or not they show promise in the pharmacotherapy of psychiatric conditions. Studies of the mechanisms of action of known psychoactive drugs in man and in laboratory animals are also in progress. Assistance in such areas as scientific documentation and data analysis is provided to investigators working in psychopharmacology.

Developmental disorders

A substantial portion of the Institute's research involves emotional and mental disorders related to growth in childhood. Such disorders take the form of neuroses, psychoses, delinquency, mental retardation, and other forms of disordered thinking, feeling, and behavior.

The importance of childhood environment for later development and adjustment has long been stressed in theory and documented by case histories. Rigorous scientific data, however, have been lacking. Among grant-supported studies is one which is now providing through study of monkeys the first important corroborative evidence that inadequate rearing, and traumas such as social isolation, do in fact disrupt normal behavioral development and lead to difficulties comparable to the personality disorders and severe mental illnesses encountered in humans. It has been shown, for example, that infant monkeys separated from their mothers at birth and deprived of physical contact with other animals develop bizarre behavior patterns—from mute withdrawal to frenzied rage. Rearing with an "artificial" wire-and-terry-cloth mother also has a distorting effect. It has been demonstrated that the capacity to learn and to relate to others is affected by childhood experience. Monkeys which suffer early psychological trauma such as the deprivation of maternal protection and warmth become inadequate and unworthy parents themselves. The concepts and methods developed in this research have already been applied by several research psychiatrists and other behavioral scientists in clinical investigations of great importance to mental health.

Juvenile delinquency

The Institute is spporting an expanding variety of studies of juvenile delinquency in recognition of the urgency of this public health and social problem area. Various disciplines are collaborating in attempts to identify causes of deviant and antisocial behavior among juveniles. Based on the knowledge that a high degree of correlation exists between delinquency and social disorganization, studies are being conducted on social disorganization in an effort to obtain information that would lead to the development of effective control measures. Additional research includes, for example, a study of characteristics of families of antisocial young children; an analysis of the relationships among community, interpersonal, and personality factors in juvenile delinquency; a study of street corner groups and the patterns by which the delinquent process develops; an evaluation of the use of drugs with disturbed children; and an assessment of the means whereby the juvenile offender can be reintegrated into society.

Aging

The skills of many investigators in the biological, psychological, and social sciences are represented in a variety of research projects on aging. A team of Institute scientists has collaborated in a comprehensive study of the symptomatology of aging, and have found that many manifestations ordinarily attributed to aging may be attributable to other causes. Social, personality, and health variables all are of considerable importance in explaining changes that occur in aging persons.

Another Institute investigator has developed an instrument called the Psychomet, which has yielded significant data on the extent to which aging results in a general slowing of mental and behavior processes. A surprising correlate of these findings has been that trends toward slowed performance may appear in relatively young men. The findings raise implications for determining the extent to which behavioral changes of advancing age may predict length of life and disease states, and may eventually have a place in early detection methods in health surveys.

Mental retardation

NIMH's research support in the area of mental retardation focuses on the psychological and social aspects of the problem. For several years a group of investigators supported by NIMH has been studying 4,000 mentally retarded hospital admissions during the period 1945–60. Each admission is being studied in terms of physical, mental, and behavioral characteristics before, during, and after hospitalization together with the medical and social characteristics of the family. The findings are expected to sharpen prognostic techniques, to furnish bases for hospital and community program development, to increase understanding of the natural history of mental deficiency, and to supply source data for further medical, psychological, and sociological research.

A number of studies are being conducted to develop and test new remedial techniques for training the mentally retarded. One particularly promising development has been the utilization of teaching machines with mentally retarded children.

Investigators are increasingly interested in the effects of social deprivation on intellectual development. Special attention is being given to the emotional and intellectual effects of residing in an institution upon the behavior of the retarded. For example, one group of investigators has found that the often reported inflexible and stereotyped behavior of retardates in experimental situations is not due to innate rigidity but to a heightened desire, springing from social deprivation, for the support, approval, and continued attention of an adult observer. Another study is being conducted to determine whether foster home care can overcome the retarded behavior frequently displayed by children reared in institutions for infant care.

Diagnosis and treatment

A large part of the Institute's research program involves studies relating to diagnosis and treatment of the mentally ill. The diagnostic studies include attempts to develop more reliable methods of personality measurement and assessment both in normal and abnormal individuals and the quantification of psychopathology in patients with psychiatric disorders. The complexity of measuring psychological and psychopathological characteristics has led to the development of increasingly sophisticated techniques of data analysis, including the use of electronic computer programs.

Research is being actively pursued on the effectiveness of a variety of approaches to the care of the mentally ill including the study of day care centers, aftercare programs for patients released from psychiatric hospitals, new methods of handling psychiatric emergencies, as well as detailed investigations of the effects of and various sociotherapeutic and psychotherapeutic approaches to the care of psychiatric patients.

The NIMH, through its programs in research, training, and assistance to the States, is proceeding to increase our knowledge of the nature, causes, and treatment of mental disease while, concurrently, working to assure that present knowledge concerning care, treatment, and prevention of mental illness is applied in a vigorous and intelligent manner. Significant strides forward have been made in the past; the prospects for further improvements in this important public health area are excellent.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

THE NEUROLOGICAL PICTURE

Health needs

For centuries a neglected field of medicine, neurology is burgeoning with discovery and progress. The National Institute of Neurological Disease and Blindness (NINDB) is participating, and sometimes leading, in this exciting growth of useful knowledge.

What is neurology? A little-known word 10 years ago, neurology is "the branch of science dealing with the nervous system, specifically with diseases of the nervous system." The nervous system includes all the nerve cells, whether grouped in the brain and spinal cord, or found singly in a fingertip.

Every thought a person has, every movement he makes, consciously or unconsciously, involves his nerve cells. Almost everyone has an occasional neurological problem—a headache, a little trouble with his eyesight, a time when he doesn't hear what is said.

But the number of Americans partially or completely disabled by neurological ailments is tragically large. An estimated 10 million are handicapped by serious neurological disorders.

Manpower

One of the first significant steps NINDB took after its founding was an assessment of the shortage of trained manpower from whom progress in knowledge about the brain and nerves could be expected. Training programs were encouraged and supported by NINDB grants.

Already the impact of Institute training programs is quite apparent. During the past 2 years, the number of full-time specialists in teaching and research in neurology increased from 139 to 287; in neurosurgery, from 58 to 113; in ophthalmology, from 64 to 128; and in otolaryngology, from 33 to 77. Thus, the Institute already has met some of the need for research personnel.

However, at least 6 percent of the Nation's population suffers from neurological impairments, 12 percent of all deaths are caused by neurological disease, and 90 percent of all totally disabled dependents receiving social security benefits suffer from neurological disorders.

Yet less than 1 percent of all certified physicians are neurologists. In private practice, there are less than a thousand neurologists and in full-time teaching or research, 287. Clearly the specialty of neurology still is vastly undermanned.

In order to meet its goal of an accelerated output of well-trained neurologists, the Institute's training program recently took important new steps. These include grants for new or improved training programs in neurology, ophthalmology, and otolaryngology. The Institute also broadened the scope of its program to support training for medical careers in organized community health services and public health, as well as for careers in research and academic medicine.

RESEARCH: ORGANIZATION

Intramural and extramural research

A brief look at the organization of this Institute reveals its national and international influence, far beyond the sphere of its own laboratories. For example, NINDB investigations in Guam, Japan, and western New Guinea have uncovered foci of high incidence of an invariably fatal disease, amyotrophic lateral sclerosis (ALS). This disease kills more than 1,000 Americans annually. From research studies in Guam, where ALS causes approximately 10 percent of the adult Chamorro deaths, information may come which will save American lives .

About four-fifths of the NINDB budget supports the Institute's "extramural programs" located in universities, medical schools, and hospitals throughout the Nation. Grants provide support for research in the neurological and sensory disorders, including blindness, and the hearing and speech fields. The training program also is financed through the extramural programs of NINDB.

About one-fifth of the annual NINDB budget supports the "intramural program" of clinical and basic research at Bethesda. A simple listing of the branches of clinical research gives some insight into the complex program: Medical neurology, surgical neurology, ophthalmology, and electroencephalography. The basic laboratories are neuroanatomical sciences, neuropathology, neurophysiology, biophysics, neurochemistry, and molecular biology.

Furthermore, intramural funds support NINDB's "collaborative and field research" area, which includes the Perinatal Research Branch (studying 50,000 mothers and their offsprings), the Laboratory of Perinatal Physiology (conducting animal studies in Puerto Rico) and the Biometrics, Epidemiology, and Special Projects Branches.

Many facets of pregnancy and newborn life are studied at the Laboratory of Perinatal Physiology in Puerto Rico. Here our scientists have closely observed more than 700 monkey pregnancies and found that the monkeys who roam the small offshore research island freely have far fewer losses of babies before birth than the monkeys in the caged colony.

The investigators also found behavior in monkey newborns which resembled cerebal palsy when the babies were examined after an artificially caused lack of oxygen. Because such a lack of oxygen sometimes occurs naturally during human delivery, a treatment which is saving monkeys is showing early value for human babies. The injury to the infant monkey brains appears to take place after the period of oxygen deprivation, and has apparently been prevented by injections of two common substances known to be important in healthy blood. These are glucose and sodium bicarbonate, and when used early during oxygen lack (asphyxia) appear to reduce the likelihood of brain damage.

Many neurological disorders have their origin during pregnancy or at the time of birth. The origin of such disorders, which result from brain injury in the earliest days of life, is difficult to determine because the existence of a brain defect may not become apparent until early childhood, often several years after the injury took place.

To study these perinatal causes of brain damage—for example, cerebral palsy and mental retardation—the Institute organized a vast project involving the collaboration of Institute scientists and 15 universities. With this project, detailed information is being obtained about the pregnancy and labor of 50,000 pregnant women.

Their offspring are meticulously observed from birth through childhood to the early school years. Attempts are being made to relate the observed defects in the children to the circumstances and events of pregnancy which may have been responsible. The study is already providing valuable information about the causes of prematurity, neonatal asphyxia, and jaundice, and the impact of these conditions upon the child's developing nervous system.

As part of the study, blood samples from all the mothers are coded and stored in a unique cold storage vault. If a child should have a problem at a later date, the mother's blood samples taken during pregnancy can be checked against more than 100 different viruses now on file.

Already, as a valuable byproduct of this virus study, scientists at NIH confirmed the identity of the virus that causes rubella (German measles). Rubella is an important source of mental retardation, deafness, and blindness. Isolation of the virus was an essential step toward the development of a vaccine. Scientists at NIH and in other laboratories are now evaluating an experimental vaccine to prevent the disease in mothers and the resulting disastrous effects on the unborn child. As research continues, similar results with others of the viruses may add to the practical applications.

Basic and clinical research

There are other ways of dividing or classifying the NINDB program, in addition to this one of intramural and extramural research.

For example, research projects sometimes separate clearly into either basic or clinical research; sometimes basic and clinical research are intimately interwoven.

The idea of clinical research, which deals with sick people, has great popular appeal. What is the safest operation for a person with cataract? NINDB carefully checked with animals the safety of an enzyme which loosens the ligaments which hold the eye lens in place and makes lens removal easier. Assured by exacting animal tests that the enzyme was not dangerous, scientists continued their research on cataract surgery in humans. Here is an example of animal research with an immediate application for clinical research.

What causes cataracts? Basic research investigators are testing a great many physical and chemical agents for possible damaging effect on the eye lens. One cause of cataract which was discovered at the Institute was the use of long-term or large doses of cortisone.

Another eye ailment which eventually blinds if untreated is glaucoma. The same corticosteroids which sometimes cause cataract also have caused glaucoma after protracted, intensive therapy. This research information alerts physicians to insist upon regular eye checks when intensive use of cortisone is carried out.

Another kind of basic research is the restudy of eye tissues with the electron microscope, with its magnification up to 100,000 times. Such super detail study of normal eye tissue is valuable for a basis of comparison with microscopic studies of eye tissue in disease.

As another example, neurochemistry is not only used in research, but also serves as a foundation for blood and urine tests for neurological diseases.

Neurological and sensory disorders

Still another way to organize research in neurology is around a particular disorder, such as Parkinson's disease, or a group of disorders, such as the neuromuscular diseases.

Many of the approximately 200 neurological disorders cluster around a symptom, such as seizures in the epilepsies. But some symptoms, such as tremor in Parkinson's disease or in multiple sclerosis, appear in more than one neurological diorder. Then research seeks the difference, for example, by use of an electronic device which records the tremors of these two ailments.

Hopefully, basic research on the brain and nerves in one breakthrough may provide clinical progress for several ailments.

For each neurological disease, certain questions turn up repeatedly as a subject of vital research:

Prevention

Repeated blood transfusions are saving babies from mental retardation or death when the mother and her husband have conflicting blood types (the Rh factor). Research supported by NINDB is following a number of babies who have had such "exchange blood transfusions." Furthermore, NINDB supports research in the field of blood conflicts which may lead to other modes of preserving the intelligence, eyesight, and hearing of newborn babies.

Early diagnosis

The NINDB has supported a long-term, nationwide program to study conservation of hearing in schoolchildren. If a first-grader is located while her hearing loss is slight, her schoolwork and social adjustment will be protected.

However, NINDB more recently has developed, in the collaborative project studying those 50,000 mothers and their babies, a speech and hearing test for the 3-year-old. The little child with a hearing loss will be detected, any remedial defects can have immediate attention, and the 3-year-old who needs a hearing aid will begin its use at once so that speech will develop normally.

Examples of progress

When something goes wrong in the brain or nervous system, neurological or sensory disorders follow. Here are some neurological or sensory problems in which the Institute conducts or supports research: (Prevalence figures are estimates by various voluntary health associations.)

Blindness and partial loss of vision account for 385,000 legally blind persons. Almost 2 million Americans are partially disabled by lack of normal vision.

In a new surgical technique, developed by NINDB grantees, liquid silicone was injected into the vitreous chamber of eyes with retinal detachment. This improved the vision in cases previously unresponsive to treatment, but a cause must be found for retinal detachment, so that it can be prevented.

A new drug, originally developed by the National Institutes of Health as a possible cancer cure, was discovered by an NINDB grantee to serve as a powerful antivirus agent when used for the treatment of virus infection of the eye. This treatment has already saved many from blindness.

Improved methods of diagnosis now reveal that approximately 2 percent of people over 40 are suffering from increased pressures within the eye—the forerunner of blinding glaucoma. Early and increasingly effective treatments are saving these potential victims from blindness.

Brain tumors offer a grave threat to the life of an estimated 500,000 Americans. When tumors invade a vital area, early diagnosis and suitable treatment provide the present hope for lifesaving.

Research has produced improved tests for early diagnosis. Progress in brain surgery under extreme body cooling (hypothermia) is saving many lives.

Cerebral palsy is a brain-centered damage to control of movement. About 550,000 persons are believed to have cerebral palsy. Particularly encouraging is the Institute's long-term, nationwide study of 50,000 mothers and their children, already mentioned.

Cerebrovascular diseases, particularly stroke, disable an estimated 1,800,000 persons with partial or complete paralysis.

Research studies include the effect of anticoagulants and continue to produce improved techniques for surgery. A new approach is testing for blocks in neck arteries as a cause of stroke, and devising methods of correcting the block.

Epilepsy, by which is meant repeated seizures or convulsions, affects more than 1 person in 200 in America or a total around 1 million people.

While no perfect antiseizure medicine has been discovered, research progress is being made in devising and testing new compounds. The physician can work out with the patient, for his type of epilepsy, the best amount and combination from a dozen to 20 medicines. A limited number of patients have had surgery which has controlled or improved their ailment.

Headache, a symptom coming from many different causes, and affecting almost everyone occasionally, is a warning to obtain a medical diagnosis.

Through research studies, treatment is being improved. A new medicine which helps prevent attacks of migraine headache was released for prescription use, recently, after careful testing by an NINDB grantee and other physicians.

Hearing disorders handicap an estimated 125,000 totally deaf persons, and about 3 million with major hearing defects.

In basic research, an Institute scientist is the discoverer of the "feedback" in hearing. Nerves were demonstrated which pass from the brain to the ear, to regulate the sensitivity of the ear to sound. This assists in the discrimination of sound messages carried to the brain. In clinical research, several NINDB grantees share credit for the development of improved operations for a common kind of deafness, called otosclerosis.

Mental retardation, due to either biological causes or problems of environment, affects an estimated 5,400,000 persons. Like several other neurological ailments, mental retardation comes from many causes, which researchers must separate and attack individually.

For example, a rare defect sometimes present at birth causes phenylketonuria or PKU. In PKU, lack of an enzyme necessary for assimilating (metabolizing) a common food protein, phenylalanine, causes severe retardation in untreated patients.

But a simple blood test makes early detection of PKU practical, and a special diet low in phenylalanine prevents retardation. Widespread use of these research discoveries could wipe out this form of mental disability.

The German measles virus, which can cause mental retardation, blindness, and deafness in unborn children, has been identified and isolated. As already mentioned, preparation of a vaccine to prevent German measles is underway, and hopefully will eliminate this source of mental retardation.

Multiple sclerosis causes various motor, speech, and sensory symptoms in approximately 250,000 young adults. Related diseases (called demyelinating because the myelin covering of the nerve is lost in patches) afflict another estimated 250,000 Americans. Although no successful treatment is known, research continues in the hope of finding a cure.

Active research is seeking possible causes through study of allergies, of viruses, and of the differing effects of climate. As causes are discovered, preventives for them will be sought.

Neuromuscular disorders currently disable about 200,000 children with muscular dystrophy, and an estimated 30,000, mostly adults, with myasthenia gravis and familial periodic paralysis. An undetermined number have myositis.

Although no effective treatment has been found for muscular dystrophy, earlier diagnosis is possible, due to research findings. More exact testing also simplifies the diagnosis of similar, but curable, ailments which can be confused with muscular dystrophy.

An enzyme which helps carry messages from the nerve to the muscle is being studied. Further research may lead to applications for care of patients, in such ailments as myasthenia gravis.

Parkinson's disease inflicts tremor and rigidity on about 300,000 to 500,000 persons, most of them in the older age group.

In spite of no known cure, and no known preventive, improvements in medical and surgical relief devised by NINDB grantees and at the Institute are helping selected patients with Parkinson's disease.

Tremors and rigidity in monkeys have been produced at the Institute by use of a chemical compound. This makes possible animal studies on the nature of the symptoms.

CONCLUSION

Highly important gains have been made in recent years in treating and preventing some of man's oldest afflictions. The pool of qualified scientists has been enlarged. Numerous well-equipped laboratories have been developed which will serve as a background for further progress in research.

Important as these gains are, they are only beginnings. New knowledge is urgently needed to diagnose, treat, and cure the millions of men, women, and children who are handicapped by disorders of the brain and nervous system.

NINDB is looking for this new knowledge in its own laboratories and through study of its own patients at the NIH Clinical Center. Global search for talent and ideas in the field of neurological and sensory diseases will continue the progress already made toward positive health as an American birthright and liferight.

THE CLINICAL CENTER

The Clinical Center of the National Institutes of Health is a 14-story, 516-bed research hospital with twice as much space devoted to laboratories (approximately 1,100 laboratory units) as to patient care areas. It was opened in July 1953.

Authorized by Congress specifically for medical research purposes, the Clinical Center does not offer general diagnostic and treatment services in the same sense as most hospitals. Patients are selected solely because they have a precise stage of an illness needed in a particular study being conducted by one of the institutes. The patients are referred by their personal physicians. Approximately 4,000 patients are admitted annually. While in the Clinical Center they receive, without charge to them, the best care known to medical science. When participation in a study is completed and their medical condition permits, patients are returned to the care of their own physicians; periodic followup examinations or treatments may be given for months or years. Referring physicians are kept fully informed about the treatment and progress of their patients.

The primary mission is to provide the specialized forms of hospital care necessary for the study of both normal and abnormal human physical and emotional phenomena. The Clinical Center is utilized by the clinical investigation programs of seven of the nine institutes. The supporting services it provides include nursing, dentistry, clinical pathology, nutrition, social work, diagnostic X-ray, anesthesiology, pharmacy, physical medicine and rehabilitation, spiritual ministry, recreational therapy, medical records, blood bank, radiation safety, environmental sanitation control, and other services found in a large, modern hospital.

In staffing this wide range of patient care services and furnishing employee health services to maintain on-the-job health of about 10,000 NIH employees, the Clinical Center employs approximately 1,700 persons. In addition to the permanent staff, there is a constantly fluctuating population of guest scientists, clinical and research associates, and consultants representing literally every professional category in clinical medicine and biologically oriented sciences.

As part of its cooperation in the training of research manpower, the Clinical Center maintains residency programs in those departments appropriate to the central service. The Institutes, in their clinical research programs, appoint clinical associates who are trained in the techniques of clinical investigation in both laboratory and patient care aspects during their limited appointments at NIH. Many of the programs utilizing clinical associates have been approved for residency credit by the appropriate specialty boards.

An average of 1,000 persons with medical, scientific, and paramedical interests visit the Clinical Center each month; of these, about 25 percent are from foreign countries and many of them represent ministries of health. The Clinical Center maintains a large auditorium which is in frequent use for national and international meetings, lectures by world-renowed scientists, and for combined clinical staff conferences.

Because some patients participate in long-term studies, every consideration is given to their comfort. A solarium is available to patients on each floor; the Center operates a library for patients; there is a recreation hall with space for beds and wheelchairs; a chapel with interchangeable altar for different faiths; and special attention is given to occupational, recreational, and physical therapy as part of a broad program of rehabilitation.

To provide the baseline of health data needed for certain studies, the Clinical Center has a normal volunteer control patient program. Selection of the health persons who participate in this program is made primarily on a medical basis and they are recruited through contract arrangements with certain churches, colleges, and welfare organizations. A volunteer may experience minor discomfort or inconvenience while participating in the research studies, but all procedures are carefully screened from the viewpoint of his safety and well-being.

The integrated laboratory-clinical investigation programs encompass many of the major causes of death and disability. The research mission of the National Institutes of Health guides the activities of many patient care services beyond levels customary in most hospitals. For example, members of the Clinical Center's blood bank staff developed the plasma-pheresis process (the removal of blood for the purpose of obtaining a fractional component of the blood and returning the balance to the donor) for the supportive treatment of children with leukemia under study in the National Cancer Institute.

Clinical Center nurses have the time, equipment, instruction, and guidance to function as effective members of the research team. Nursing research is an integral part of day-to-day patient care activities. This type of study has helped in assessing the value of the latest electronic monitoring system for patients requiring close and constant physiological observations.

The social work department also is involved in the development of the total clinical research program. Increasingly, clinical investigators request social workers' collaboration in the study and treatment of the emotional and social components of long-term illness.

The anesthesiology department in the Clinical Center is involved in the performance of complex and protracted procedures in heart surgery, brain surgery, and cancer surgery.

Other interesting activities include: The use of comprehensive electronic monitoring and recording systems in a new surgical wing which enables surgeons to provide the most advanced techniques for patients and to collect valuable research data previously unobtainable; the demonstration of closed-circuit television as a teaching tool for inservice training of nursing staff; advanced types of radiologic perception in the use of radioisotopes in "brain scan"; improved efficiency and quality control through automation of laboratory procedures in clinical pathology; use of a whole-body radiation counter capable of recording separately the amount of radiation in 18 areas of the human body which permits investigators to conduct more sensitive, more accurate, and more detailed studies involving low levels of radiation; application of electromyography as a diagnostic service in evaluation of patients with neuromuscular disorders; formulation of radioactive pharmaceuticals for diagnosis and treatment; development of new nutritional procedures for revised treatment of some metabolic diseases; and application of environmental sanitation measures to control hospital infections and other hazards. These are examples of activities which are research today but will become routine tomorrow.

Findings related to improved hospital utilization and patient care are communicated broadly as members of the staff lecture and publish frequently.

DIVISION OF BIOLOGICS STANDARDS

FUNCTION AND RESPONSIBILITIES

The primary function of the DBS is the administration of those provisions of the Public Health Service Act that pertain to the safety, purity, and potency of biological products. As a result of such control, safe, pure, and potent biological products are made available to the physician for use in the prevention, treatment, or cure of diseases or injuries of man. These include the vaccines, antitoxins, and therapeutic serums, as well as human blood and its derivatives. Developed, for the most part, from pathogenic or potentially pathogenic microorganisms, these substances require careful control in order to minimize safety hazards which might occur in the course of processing, and to insure final products of satisfactory potency. Accuracy is essential in every step.

The large-scale support which has been given medical research in recent years is reflected in the development of improved methods of immunization and new therapeutic measures. The increasing public interest in these discoveries, has, in turn, given competitive stimulus to the development of new products. Thus, the time interval between research and product availability has been materially reduced. The Division, charged with the responsibility to develop regulations for the commercial production of these products has necessarily expanded its own research, testing, and control efforts.

The research programs of the Division's six laboratories—Control Activities, Bacterial Products. Biophysics and Biochemistry, Blood and Blood Products, Viral Immunology, and Virology and Rickettsiology—include a diversity of projects, many of immediate practical urgency, and all having direct relation of the prime responsibility of the Division. The scope, direction, and intensity of these programs are dictated by the need to provide essential information for the development of requirements and regulations for new biological products, as well as improvement of tests for established products.

Basis of control

The control of biological products is based on a system of licensure. This system includes the issuance by the Secretary of Health, Education, and Welfare, of both establishment licenses and product licenses, following determination by the Division that the prescribed standards have been met. These standards are set forth in regulations which are continually reviewed by Division scientists for adequacy, and revised as scientific knowledge advances.

The Laboratory of Control Activities, coordinates, with members of the other laboratories, the eligibility of establishments and of biological products for license. This determination is made on the basis of the integrity of management and technical personnel, the physical facilities for manufacturing and testing of products, and the scientific and professional qualifications of personnel.

Once a product is licensed, continuing surveillance is maintained by periodic inspection of the manufacturers' facilities and production methods, review of records of production and testing, and testing in the Division's laboratories of representative samples of the products. Over 7,000 control tests were carried out during 1962. The results served as a basis for the release or rejection of the more than 5,000 lots of products submitted to the Division by manufacturers during this period. The testing procedures include a variety of tests, ranging from relatively simple sterility tests to complex and potency determinations and safety tests.

To assure that every lot of a product is of acceptable consistency and uniform potency, standard and reference preparations are developed by the Division. Seventy-five such preparations are now maintained and approximately 6,000 vials are distributed annually to research and control laboratories of licensed manufacturers, health departments, and universities in this country and abroad.

Control supported by program of research

Basic research on the physical and chemical factors that determine the biological properties of viruses, bacteria, and rickettsia, as well as their host cells, is an integral part of the Division's research program. The Laboratory of Biophysics and Biochemistry is engaged in the study of biophysical methods of analysis, including ultracentrifugation and electron microscopy, supplemented by specialized techniques for concentrating and purifying the micro-organisms for study. An immediate objective of the Laboratory is the development of methods for rapid characterization of newly identified viruses.

Other biophysical studies in progress include an investigation of the mechanism of thermal inactivation of viruses, determination of the relative susceptibility of animal viruses to photodynamic inactivation, development of methods for differential inactivation of simian viruses in suspensions of live attenuated polioviruses, and the study of the effects of various physical and chemical stresses upon metabolism of tissue culture cells.

The study of photochemical processes affecting survival of viruses has led to the development of a photosensitization technique for differentiating between parent and progeny virus in cell cultures. This has made it possible to detect multiplication of poliovirus in nonprimate cells that were previously thought to be refractory to infection. This finding has some bearing on the developing concepts of the relationship between viruses and their animal hosts.

Basic information obtained in studies of this type aids in understanding the problems encountered in production, testing, and control of biological products of microbial origin.

Research in the Laboratory of Bacterial Products is related to the continued quality and improvement of bacteriological products and to the development of methods for the control of new ones. Products studied include cholera, pertussis, typhoid, and BCG vaccines; diphtheria and tetanus toxoids; antibacterial antitoxic serums; and allergenic products.

Cholera vaccine, one of the first immunizing agents to be introduced in this country, was licensed for commercial use in 1910. The Division takes an active part in the World Health Organization's program for the development of international recommendations for cholera vaccine to facilitate the exchange of vaccines between countries in times of emergency. The disease is still prevalent in some parts of the world, and with the present day speed of international travel could constitute a real threat if introduced into receptive areas.

Experimental work is directed toward the development of quantitative potency tests for laboratory evaluation of cholera vaccine and the establishment of a U.S. standard vaccine. This research is coordinated with the SEATO cholera research project and with international efforts to determine the relation between laboratory evaluated potency and human protection.

Experience has shown that answers to some health problems in this country can often be more readily investigated in other parts of the world where environmental conditions present opportunities for resolution. In New Guinea, a study has been undertaken by the Division in cooperation with Australian workers on the possibility of prevention of tetanus in the newborn—a serious cause of death among the newborn in that area—by prior immunization of the mothers thereby also providing an opportunity for studying the dynamics of antibody response in antitetanus inmmunizations.

With the increasing availability of immunizing antigens there has been a trend toward the combination of several antigens in a single product, although the preparation of these products is a complex process. This is especially true of the quadruple antigen vaccine which is used in pediatric practice. This product is composed of diphtheria and tetanus toxoids combined with pertussis (whooping cough) and poliomyelitis vaccines. Studies conducted by the Division on the stability of this product revealed that there was a significant decrease in the potency of the pertussis component during the prescribed dating period. The reasons for this are, as yet, obsecure. However, as a result of the investigations, the dating period for this product was shortened and the potency requirement of the pertussis component was increased so that it would not fall below the required minimum level even when the product is exposed to variable market conditions.

Live poliovirus vaccines

Complex problems have emerged during the past several years in the process of evaluating the results of widespread use of the live poliovirus vaccines. While these were largely epidemiological, the extent of related studies carried out in the Division's laboratories indicates the scope of its research on control methodology for such candidate products. The major portion of this work is the responsibility of the laboratory of Viral Immunology.

Types 1 and 2 of the Sabin strains of the live, oral poliovirus vaccine were licensed during the fall of 1961; type 3 was licensed 6 months later. The delay in licensing the type 3 strain—genetically the most labile of the three—was caused by difficulties encountered under manufacturing conditions in the production of five consecutive lots of vaccine that would meet the requirements for a low degree of neurovirulence in monkeys.

The monkey neurovirulence tests required for all three types of live poliovirus vaccine involved extensive laboratory study. Approximately 150 tests in 4,000 monkeys were made on vaccine samples submitted by the manufacturers. This testing provided a wealth of information and experience that has been invaluable in judging the validity of subsequent tests on individual lots of vaccine.

Other vaccines

Influenza.—A number of variants of the influenza virus strains continue to appear. In cooperation with other interested laboratories, the Division studies these variants with a view to the possible selection of an additional virus strain or strains for representation in the vaccine. In December 1962, it appeared that the incorporation of new strains in the vaccine would again be called for and appropriate studies were initiated by the Division in cooperation with manufacturers and specialists in this field.

Results obtained in the Division's Laboratory of Virology and Rickettsiology indicated that a shift in antigenic composition in some of the 1961–62 Asian strains had occurred. Antigenic analysis of influenza B strains recovered in the winter of 1961–62 in outbreaks of influenza in the United States and Canada indicated a clear, but relatively small, antigenic difference between the recent strains and the older strains contained in the current vaccine. As a result, it has been recommended that one of the new A2 variant strains and one of the recent B strains be incorporated into the vaccine manufactured for the 1963–64 influenza season.

Measles.—At the 1961 international conference on measles immunization, initiated by the Division, investigators from 22 countries presented clinical and experimental data on measles immunizations clearly indicating that prophylaxis against measles could be accomplished.

The subsequent development of regulations for measles vaccines by the Division called for an extensive array of controls, since three products were involved—live measles vaccine, inactivated measles vaccine, and standard gamma globulin for use with the live vaccine.

The regulations cover the characteristics of the measles virus strains to be used in the vaccine; the exclusion of adventitious agents from the virus fluid used in manufacture; the employment of a variety of animal and tissue culture test methods; the demonstration of satisfactory clinical use of the vaccine, including clinical effectiveness; and the stability of the live virus vaccine strains in terms of capacity to revert to significant virulence in man. Both the killed and live virus measles vaccines were licensed in the spring of 1963.

The Division's Laboratory of Virology and Rickettsiology has added materially to knowledge on the use of live attenuated measles virus vaccine through its studies in west Africa. These, undertaken as a collaborative venture by the

Division, the Ministry of Health of Upper Volta, and the Agency for International Development, have demonstrated that Voltan children respond in the same manner as American children to the live vaccine, whether given alone or in combination with gamma globulin. Because measles is one of the serious diseases of Upper Volta, with mortality rates running as high as 50 percent at times, and because the Volta health officers and the people do not object to the mild illness which is common when attenuated virus is given without gamma globulin, the attenuated vaccine alone was given to all susceptible children under 3 years of age. This represents the first attempt to eradicate measles from a nation. At the termination of the study in February 1963, over half a million children in Upper Volta had been vaccinated.

The vaccine was administered parenterally by jet injection by Voltan teams traveling through the entire country, district by district. Each team consisted of three Voltans, employed by the Ministry of Health, equipped with a jeep, two jet guns, an electric generator for operating the guns, and a portable refrigerator for transportation of the vaccine. Each of the eight teams were trained, advised, and assisted by the three-member team from the Division.

The ultimate success of the large-scale immunization program will be judged by the reduction in measles during the next epidemic season; however, it is already apparent that the experience has provided worthwhile information on how measles immunization can be accomplished in developing areas of the world.

Adventitious agents

The Division has also been concerned with adequate procedures for examining vaccines manufactured in tissue culture systems for the absence of adventitious agents, such as SV–40, one of the 40-odd simian viruses encountered during the preparation of monkey kidney cell culture vaccines. Since some of these agents cause diseases in animals, despite the fact that with few exceptions, the role of these viruses in the production of human disease is unknown, the Division requires their exclusion from all such commercial vaccines. Identification and elimination of these occult viruses constitutes a vexing problem. Since in many instances, they cannot be detected by routine tests normally employed in vaccine production and control, elaborate test systems must be devised.

SV–40, for example, first identified in 1960, was found in 1961 to be present in residual amounts in certain lots of killed polio vaccine, as well as in adenovirus vaccine. Although it is not known to produce disease in man, nor does its presence in the vaccines prevent the development of immunity against the disease in vaccinated persons, it has been found to produce cancer in newborn hamsters and, therefore, has become emotionally linked with cancer in human beings, although no such relationship has been demonstrated.

Since May 1961, all lots of poliomyelitis and adenovirus vaccines released have been tested for SV–40, and only those free of this agent have been cleared by the Division for commercial use. Since killed poliomyelitis vaccine can be manufactured free of SV–40, the availability of adequate quantities of vaccine was not seriously curtailed. However, few manufacturers at that time were in a position to begin immediate testing for this virus, a testing program was carried out by the Laboratory of Viral Immunology which helped to assure adequate supplies of poliomyelitis vaccine following the May 1961 decision.

In order to determine whether conditions of trapping, handling, and shipping were important factors in obtaining virus-free monkeys, Division investigators went to India to supervise the handling of rhesus monkeys from the moment of capture to their arrival at NIH laboratories. Their findings confirmed that SV–40 occurs naturally in the free-ranging rhesus monkey.

The production and testing problems posed by adventitious agents indicates a need for tissue culture cell systems free of contaminating viruses which can be used with full confidence in vaccine production and testing. An example of such a system is the continuous cell line derived from cercopithecus monkey tissue which has been developed in the Division's laboratories.

The Biologics Standards-Cercopithecus-1 (BS–C–1) cell line was initiated in March 1960, from kidney tissue of *Cercopithecus aethiops* by the Laboratory of Virology and Rickettsiology. It is now in its 125th passage and is considered to be an established cell line. Cultures have been sent to the cell bank committee (sponsored by NCI) for characterization and subsequent storage at the American type culture collection. The BS–C–1 line is unique in that its chromosomal pattern and virus susceptibility have been studied in concert since early passage levels. Findings indicate that while the chromosomal pattern of the cells changed the cells have not changed their sensitivity to SV–40. In addition to the multiplication of measles and attenuated polio viruses 1, 2, and 3, in BS–C–1 cells it has been shown that this line will support growth of Rift Valley fever virus, Rous sarcoma virus, O'Malley's A–1 agent, Coxsackie A9, and simian viruses 1, 4, and 5. Preliminary data suggest that the line may be useful in basic studies with epidemic typhus rickettsiae. The cell line has come into widespread use in the scientific world; 46 research and industrial laboratories in North America, Europe, Asia, and Australia have been supplied on request with seed cultures.

Human blood and derived products

The various research projects in the Laboratory of Blood and Blood Products have as their goal the improvement of testing procedures for the control of biological products derived from human blood. These projects cover all phases of blood collection, processing, shipment, and storage. Investigations encompass not only improvements for existing control procedures but are directed toward the perfection of tests for new products.

Studies are being carried out on the various components of the complex blood coagulation system. Some of the products under development have immunological or biological activities for which there are no established test criteria. The staff is engaged in research on some of the fundamental characteristics of these protein components to gain information on which control tests may be based. Improvements have been made in the method of preparation of a plasminogen-free fibrinogen; an important accomplishment since it brings one step closer the goal of control tests for the coagulation system.

Other research interests include studies of freezing, storage at various low temperatures, thawing, and/or drying of the many elements of whole blood and the protein fractions of plasma. Specific investigations within this broad field are undertaken to obtain data on which to base the stability of products.

For many years, the Laboratory has maintained an active research interest in the effect on the properties of whole plasma and the individual plasma proteins of time, light, container material, temperature fluctuations, and other factors. Normal serum albumin was placed on such a long-term study 8 years ago. The subtle changes which occur are taken into account in establishing a dating period schedule for this product.

Immunological studies related to the identification and quantitation of antigens of red blood cells and other elements, and of the antibodies which occur in blood are being carried out by the Laboratory. Many control tests still have an empirical basis. An ultimate goal of these investigations is the establishment of control tests which will result in quantitative expressions directly related to the immunological properties being measured.

DIVISION OF RESEARCH FACILITIES AND RESOURCES

The Division of Research Facilities and Resources administers NIH extramural programs supporting research efforts on an institutional or regional basis. As its name implies, the Division specializes primarily in providing research resources and centers, construction, animal facilities, trained assistants, and general research support to the life scientists and research clinicians who rely so heavily upon major scientific tools and methods.

Specifically, the Division aids institutions in the construction of facilities for use in health-related research; provides general clinical research centers to further the application of basic scientific facts in clinical research; increases the availability of animals including primates; supplies a number of computer, biomedical engineering, and other special resources designed to provide institutions or regions with major facilities for research support of interest to many investigators; and supports health-related research at professional schools and other institutions heavily engaged in biomedical research, for the expansion of institutional potentials.

CONSTRUCTION PROGRAM

The oldest of the five programs supporting health-related research and research training provides for construction and equipping of laboratory facilities, seeking to alleviate a highly critical shortage of working space for research scientists. The origin of this program is in Public Law 835 which added title VII to the Public Health Service Act in 1956. After being renewed three times at a level of $30 million, a fourth renewal for 3 years beginning in fiscal year 1963 raised the annual authorization to $50 million. This amount is matched by funds from private sources on at least a 50–50 basis. Awards are made for the construction of health research facilities only within the context of a meritorious ongoing program of research of interest to basic or medical life sciences.

During the past 7 years, appropriations for this program have totaled $230 million. More than 1,400 applications have been received and processed. A total of 1,039 grants has been awarded to 360 institutions in 49 States, the District of Columbia, and Puerto Rico. At the beginning of January 1963, 431 projects, representing a Federal investment of $71,305,841, had been completed. About 230 additional new facilities are in various stages of progress.

On an institutional basis, funds for construction have been distributed as follows: For research facilities in medical schools, $117,588,467; in dental schools, $2,953,415; in schools of osteopathy, $5,469; in schools of public health, $6,231,978. Research facilities in heatlh-related areas of other schools, such as pharmacy, veterinary medicine, chemistry, and the biological sciences, $55,739,123; and research facilities to other public and private institutions (chiefly hospitals) engaged in health-related research, $47,459,103. Of these funds, 46 percent has been allocated to non-Federal public institutions and 54 percent to private nonprofit institutions.

In addition to the amount allowed for construction of buildings or portions of buildings devoted to health-related research, awards may provide for a portion of the cost of new equipment. Thus the program presents a powerful stimulus for institutions engaged in research, not only to build new structures but to design and equip them for modern biomedical research. At the same time it encourages them to seek other funds to match those granted by the Federal Government.

As the health research facilities program developed, it became increasingly apparent that institutions needed help not only with funds but with their construction planning. The special demands encountered in providing for the research construction program review and evaluation required establishment of an architectural and engineering office within the Division. Staff architects and engineers now review and offer advice on all construction plans that are submitted with applications. This insures facilities that are best suited to the type of research to be conducted and provides the maximum useful laboratory space and equipment for the taxpayers dollars invested.

GENERAL CLINICAL RESEARCH CENTERS

These centers are "general" in that they support scientific investigators who share in a multidisciplinary, broad, integrated attack on a variety of medical problems. The General Clinical Research Centers Branch of the Division provides a broad program of support including renovation of the hospital unit to be used as the center, "core" laboratory facilities or diet kitchens in close proximity to the clinical research ward, costs of equipment and supplies, operational expenses, and hospitalization of patients who are carefully selected for their role in providing data for contemplated research.

As of March 1963, awards had been made for 60 NIH-sponsored general clinical research centers in the United States, of which 38 were admitting research patients, with the other 22 in various stages of preparation.

The general clinical centers permit a wide variety in the types of studies conducted. Forty-eight of the centers are adult or mixed adult-children centers; 10 are for children only, 1 is solely for the study of premature infants, and 1 (at Albert Einstein College of Medicine in New York City) is a center for acute problems, studying shock, trauma, burns, sepsis, and preoperative and postoperative patients.

Many general clinical research center projects are barely underway, but results already published attest to the long-term value of the work being done. Disease categories investigated cover a wide range of basic clinical scientific problems including basic problems in heart disease, cancer, stroke, and kidney function. Such centers are of considerable importance to the development of clinics in this country.

ANIMAL RESOURCES

The conduct of biomedical research ultimately depends upon the supply, quality, and homogeneity of the biological materials used in the program. In no instance is this statement more true than in the case of the larger laboratory animals, especially those most closely related to the human—the primates.

The regional primate research centers program, formerly a responsibility of the National Heart Institute (NHI), was transferred to the Division in July 1962 and forms the nucleus of the Division's Animal Resources Branch program. During the first 2 years under NHI, funds made available permitted the establishment of four primate centers, at the University of Oregon, the University of Wisconsin, University of Washington, and Emory University. In fiscal year 1962, three new awards were made, one each to Harvard University, Tulane University, and the University of California.

Each of the seven awards provides two grants, one for total construction costs including land, and one for operating costs for a period of 7 years. Total amount awarded for construction as of June 30, 1963, was $14,080,510. The terms of the awards require each institution to serve as a 'host" establishment, not only for fiscal management but to provide an academic environment of high standard for resident and visiting scientists.

Although each center has its own program, six are regional centers committed to providing facilities for a broad scope of disciplines using primates in research. The seventh, at Davis, Calif., will be a National Primate Conditioning Center, committed to investigations on the primate itself.

Currently, the Animal Resources Branch has three main objectives:

(1) To support the primate centers program;

(2) To develop a national effort to provide the types, quantities, and quality of any species of animal needed for biomedical research; and

(3) To determine optimum condition for laboratory animal care, including their safety and medical treatment.

Facilities and services supported by this program serve as focal points in universities, hospitals, and other institutions providing unusual and highly specialized research services or materials to many departments and disciplines, resources which would be too costly or too difficult to obtain for the single investigator. The program began in fiscal year 1962 with authorization of $5 million for computer resources and was extended the following year when an additional $6 million was authorized and greater program latitude was allowed.

Seventeen computer centers are currently supported. Here vast amounts of data are processed in an incredibly short space of time, permitting evaluation of complex experiments and massive clinical studies.

Another important step was taken recently through a cooperative arrangement between NIH, the National Aeronautical and Space Administration, and Massachusetts Institute of Technology, to evaluate the potential of the laboratory instrument computer (LINC), especially designed as a small laboratory-located, high-speed analog-to-digital converter for the health-related sciences.

One established computer resource has demonstrated not only its effectiveness for research projects of the university medical center in which it is located but for the projects of several other institutions with whom cooperative arrangements have been made for part-time assistance. Included are State mental hospitals, Veterans' Administration hospitals, public health departments, a number of medical schools and voluntary health agencies. Typical studies for which the resource has been used include the monitoring of fetal heart sounds, analyzing the probabilities of surgical risks, studies of diseases resulting from air pollution, analyzing electroencephalographic records, correlating the relationship of blood pressure and tranquilizer dosage, and the study of therapeutic methods for various types of cancer.

Although program emphasis thus far has been preponderantly oriented toward developments in computer technology and computer usage for health-oriented research, it is expected that increasing attention in the future will be given to other types of resources. All will be designed to aid institutions or regions to advance or improve their research capability and thus contribute powerfully to a combined multicategorical attack on the dread diseases. It is also expected that many scarce research materials will be made available in sufficient quantity. For example, thousands of enzymes regulate the chemistry of cellular processes within the human body, but relatively few can be purchased for study purposes. In order to meet this special need the first large-scale enzyme and biopolymer resource has been established in Boston.

The first NIH-sponsored biomedical engineering resource was dedicated at Northwestern University in mid-February 1963. This resource was designed to extend the parameters of the biological area by an infiltration of the science of engineering in all its forms into the study and measurement of biological phenomena. There a new technique employing acoustical principles with ultrasound waves used much like X-radiation has been developed to examine soft tissues of the body and study lesions of the heart and blood vessels.

Another type of special research resource will aid research on communications with increased attention to methods of data processing.

GENERAL RESEARCH SUPPORT

In 1959, as part of an appraisal of the impact of its grants program on recipient institutions, the National Institutes of Health undertook an intensive short-term study of 20 medical schools. All reported considerable expansion in research activities over the past few years. They labeled this expansion as "distinctly advantageous," contributing to widespread advancement of scientific knowledge, enhancing the quality of education, elevating the stature of their faculties, and providing new strength to their schools. Nevertheless, most schools identified a number of problems resulting from funds provided in the form of restricted gifts and grants, particularly those from Federal agencies.

To provide better support balance, a program of grants for general research support was instituted. These are distributed on a pro rata basis of the biomedical research already underway in the institution. Such grants were not given to finance specific projects but were for use by grantee institutions to provide new strength to research and research training programs in ways judged to be most effective for the institution—subject, of course, to those general guidelines and policies affecting all PHS grants.

First awards under the new program were made in January 1962. By July 1 a total of $20 million had gone to 86 medical schools, 49 dental schools, 12 schools of public health, and 6 schools of osteopathy. In 1963, $30 million was made available and the general research support program now permits (upon the satisfaction of certain criteria) the extension of support to schools of pharmacy, nursing, and veterinary medicine, and to research institutes, centers, certain laboratories, and other nonprofit organizations heavily engaged in health-related research.

General support awards are made according to formula and represent a percentage of the total amount of Federal research project grants and contracts awarded to institutions, plus a somewhat larger percentage based on an institution's available research funds received from non-Federal sources. These grants are specifically intended to enable institutions to meet emerging opportunities in research, to explore new and unorthodox ideas, to recognize and support scientific talent earlier, and, in general, to use funds flexibly and in ways which will attract additional non-Federal support for health-related research. Thus, they are provided with unprecedented opportunities for cultivating scientific excellence and for building long-range institutional strength in the health sciences. That they have been able to do this in fact is attested by information obtained from early reports, visits to the schools, and many informal channels.

One school, for example, established and staffed a new experimental endocrinology laboratory. Within the next year or so, salaries paid now from the grant will be picked up on the university budget, thus releasing general research support grant funds for the development of other research activities. This school also supported with the general research support grant funds a new animal surgery program for research, established an instrument development shop for the research support of several basic science departments, and undertook a pilot study on the breeding of animals for research.

Another school appointed three top-level research professors in 1962 and engaged a fourth to join the staff in 1963. Meanwhile, the research potential of several faculty members was increased by putting them on a 12-month salary instead of the usual 9. A third institution established three new divisions of wholly independent research activities. The same grant provided basic salaries for a number of professionals and paid the cost of needed new equipment.

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